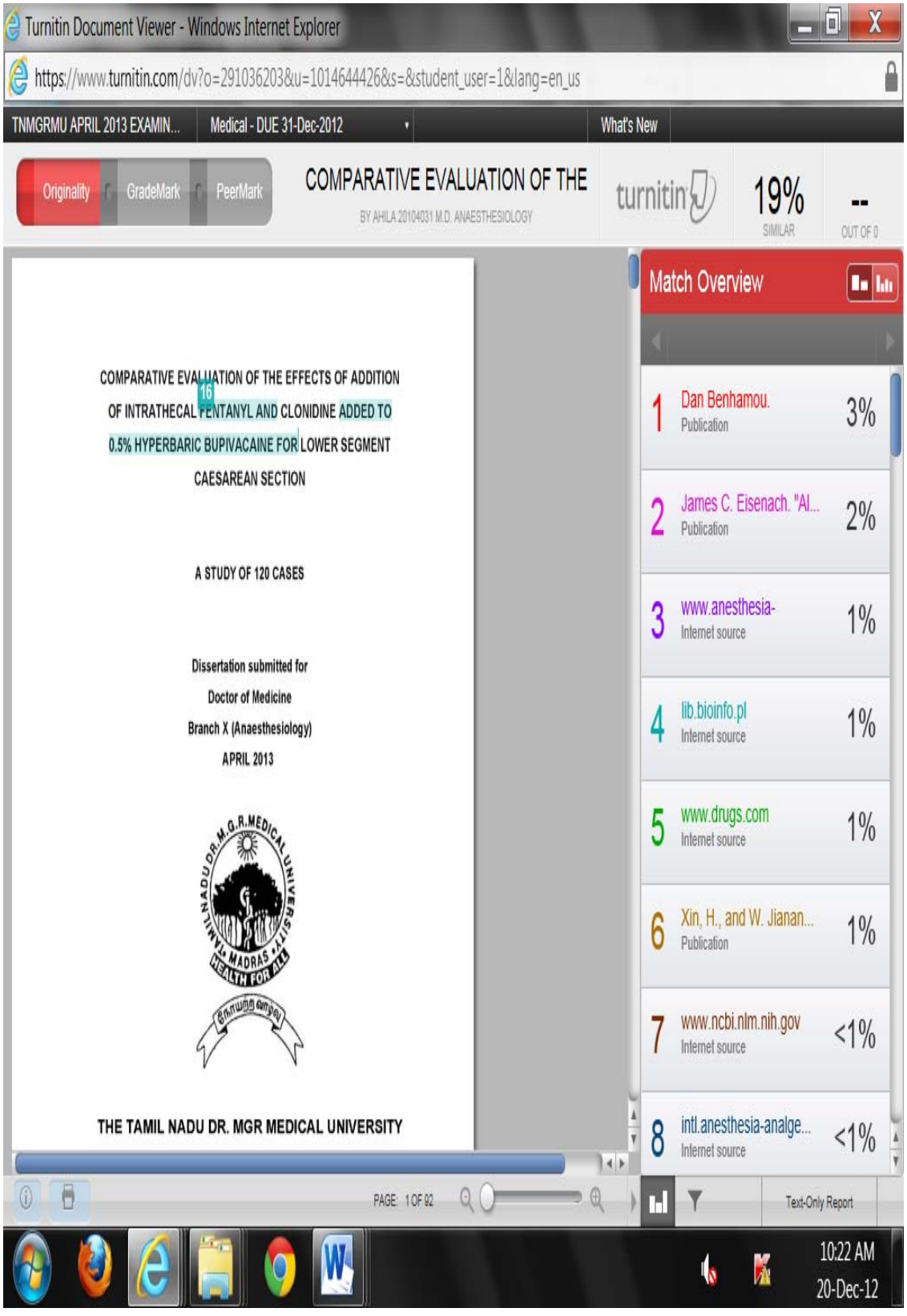
COMPARATIVE EVALUATION OF THE EFFECTS OF ADDITION OF INTRATHECAL FENTANYL AND CLONIDINE ADDED TO 0.5% HYPERBARIC BUPIVACAINE FOR LOWER SEGMENT CAESAREAN SECTION

A STUDY OF 120 CASES

Dissertation submitted for
Doctor of Medicine
Branch X (Anaesthesiology)
APRIL 2013

THE TAMIL NADU DR. MGR MEDICAL UNIVERSITY
CHENNAI.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This is to certify that the Institutional Ethical Committee of this College unanimously approves the Thesis /Dissertation/ Research Proposal submitted before this committee by Dr. K.AHILA, a **POSTGRADUATE IN ANAESTHESIOLOGY** in the Department of **ANAESTHESIOLOGY**, of Tirunelveli Medical College /Hospital, Tirunelveli titled **"COMPARITIVE EVALUATION OF THE EFFECTS OF ADDITION OF INTRATHECAL FENTANYL AND CLONIDINE ADDED TO 0.5% HYPERTARIC BUPIVACINE FOR LOWER SEGMENT CAESAREAN"** registered by the IEC as 092/ANES./IEC/2011 dated. 12.8.**2011**. The Investigator is hereby advised to adhere to all the stipulated norms and conditions of this ethical committee.

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DECLARATION

I, **Dr. K. Ahila**, declare that the dissertation entitled "**Comparative Evaluation of the Effects of Addition of Intrathecal Fentanyl and clonidine added to 0.5% hyperbaric bupivacaine for lower segment caesarean**" has been prepared by me.

This is submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment of the requirement for the award of M.D. degree branch X (Anesthesiology) degree examination to be held in April 2013.

Place : Tirunelveli
Date :

Dr. K. Ahila

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TABLE OF CONTENTS

INTRODUCTION

Relief of Pain is purchased always at a price – Ralph Waters.

"For all the happiness mankind can gain is not in pleasure but in rest from pain". – John Dyrden.

The aim of anesthesiology as a science is the removal of pain temporarily started initially with pain relief for surgeries, extending now to post operative pain relief, relief of chronic pain and cancer pain. Spinalanesthesia plays in important role of alleviating pain intra-operatively, extending sometime into postoperative period also. The entry of Corning's needle in 1885-into the subarachnoid space paved the way for the greatest leap into spinal anaesthesia. His words "Be the density of this observation, what it may have seemed to me on the whole, worth recording. This opened the prologue for the word "spinal anaesthesia". Cocaine was the drug first used experimentally in dogs. In men the first spinal anaesthesia was conducted by "August Bier" on 16.8.1898 with cocaine 3 ml as 0.5% solution followed by Matas in America and Tuffier in France.

Spinal anesthesia for caesarean section has always enjoyed popularity as it eliminates the complication of pulmonary aspiration and avoids the problem of difficult tracheal intubation observed with general anaesthesia. Other advantages of this technique are its simplicity, rapid onset and dependability.

The demonstration of opiate receptors in substantia gelatinosa of spinal cord (Yaksh and Rudy 1976) has created interest in the intrathecal administration of opiates. The use of intrathecal morphine for providing postoperative pain relief in caesarean section was started in the year 1988 by EzzazAboulesish et.al. The advantages of neuraxial opioids over neuraxial local anesthetics are that it produces prolonged, intense,

selective, segmental analgesia without motor blockade and sympathetic dysfunction.

Opiods and local anesthetics administered together have a potent synergistic analgesic effect. Intrathecal opiods enhance analgesia from subtherapeutic dose of local anesthetic and make it possible to achieve successful spinal anaesthesia using otherwise inadequate doses of local anesthetic. The α_2 adrenergicmechanism have been exploited for more than 100 yrs. Vetenarians have used α_2 agonist for many years for regional analgesia, but the experience with these agents in humans, dates back only slightly more than 10 years.

In 1984 Tamsen, Gordh after testing neurotoxicity in animals and then injected a parenteral preparation of α_2 agonist clonidine, epidurally intwo patients with chronic pain. Since then the complete toxicologic assessment in animal studies has suggested that clonidine is safe for Intrathecal use.

AIM OF THE STUDY

1. To evaluate the effects of fentanyl and clonidineadded to Bupivacaine, for caesarean section in spinal Anaesthesia
2. To evaluate the duration of analgesia by comparing two groups.
3. To evaluate the hemodynamic effects, post-operative sedation and neonatal outcome between the two groups.

ANATOMY OF SUBARACHNOID SPACE

Subarachnoid block means privation of senses not necessarily implying loss of consciousness.

APPLIED ANATOMY OF VERTEBRAL CANAL

The vertebral canal extends from foramen magnum to the sacral hiatus. It protects the spinal cord. Vertebral canal is formed by 7-cervical, 12-thoracic, 5-lumbar, 5-sacral and 4-coccygeal vertebrae. Each vertebra is composed of a 'body' separated from the adjacent vertebra by intervertebral disc and 'vertebral arch' formed by pedicles and laminae, which surround and protect the cord laterally and posteriorly.

VERTEBRAL LIGAMENTS BOUNDING THE CANAL

1. Supraspinous ligament – passes longitudinally over the tips of spinous processes from C_7 to the sacrum.
2. Interspinous ligament-joining the spinous process together.
3. Ligamentum flavum-Running from laminae to laminae, composed of yellow elastic fibres. Half of the posterior wall is composed of the bony laminae and half by the ligamentum flavum. They become progressively thicker from above downwards.
4. Posterior longitudinal ligament-on posterior surface of bodies of vertebrae.
5. Anterior longitudinal ligament-runs along the front of the vertebral bodies.

There are seven projections from these vertebral or neural arches.

They are:

a) Three muscular processes – two transverse and one spinous-for the attachment of muscles and ligaments and
b) Four articular processes – two upper and two lower – which in the lumbar region, prevent rotation but allow limited flexion and extension between contiguous vertebrae.

Vertebral canal formed by these structures, has deficiencies posteriorly in the midline, called inter laminar foramina, which enlarge in flexion accessible for the passage of spinal needle. The direction of spinous process determines the direction of the spinal needle.

SPINAL CORD

It is the direct continuation of medulla oblongata extending from upper border of atlas to 1st lumbar vertebra, below which there is leash of nerve roots termed caudaequina. Spinal nerves are 31 pairs totally.

8 - Cervical

12 – Thoracic

5 – Lumbar

5 – Sacral

1 – Coccygeal

Each of the spinal nerve is composed of anterior and posterior roots uniting at the inter vertebral foramina and form a nerve trunk.

Membranes covering the spinal cord from without are duramater, arachanoidmater and piamater. Dura and arachnoid end at S_2 level.Piais closely applied to the spinal cord.

Blood Supply

It is from the anterior spinal artery which is a branch of vertebral artery and also by a pair of posterior spinal arteries which arise from posterior inferior cerebellar arteries. There is no anastomosis between these arteries.

Spinal Veins

The spinal veins are arranged into anterior and posterior plexus which are draining into vertebral, azygos and lumbar veins.

Cerebro Spinal Fluid (CSF)

It is the ultrafiltrate of plasma from choroidal plexus of lateral ventricles with a pH of 7.4.The amount of cerebro spinal fluid in spinal canal is 75 ml with a pressure of 70-170 mm of water in lateral position.

It contains 20-40 mg % protein

45-80 mgs% sugar

0-5 lymphocytes / cmm normally

An important factor that determines the spread of drug in CSF is the specific gravity of the drug in relation to that of CSF (baricity) which is 1.003-1.009 (average 1.004). Hyperbaric solution is one which is denser than CSF at 37^0C.

PHYSIOLOGY OF SUBARCHNOID BLOCK

Subarachnoid block implies temporary interruption of nerve transmission within the spinal space by injection of drugs into the space. The blockade occurs in the order of first preganglionic βfibres, temperature, pain, proprioception and then motor fibres.

Factors controlling the extent and duration of anaesthesia

1. Specific gravity of the solution – the most important
2. Position of the patient during and immediately after injection
3. Site of injection
4. Volume and concentration of the solution: increasing the dose and concentration prolongs the effect.
5. Patient factors like age, height and pregnancy.

Effects on cardiovascular system

The most important physiological response to spinal anesthesiainvolves the CVS due to the combined effects of autonomic denervation and vagal nerve innervations at higher levels. βfibres are more sensitive than alphafibres causing a higher sympathetic block (zone of differential blockade) resulting in vasodilatation and a fall in blood pressure especially if a substantial number of thoracic segments are blocked. Due to Bainbridge reflex, the fall in blood pressure is associated with bradycardia. Blockade of cardiac sympathetic fibres is from T_1—T_4, an additional factor that causes bradycardia.

Effects on respiratory system

Respiration is not depressed normally. High spinal can-cause paralysis of intercostals muscles but resting tidal volume, maximum inspiratory volume and negative intrapleural pressure and also the phrenic nerve are unaffected. Hypoxia may accompany hypotension and is corrected by oxygen via face mask.

Metabolic and hormonal effects

Spinal anesthesia blocks hormonal and metabolic responses to nociceptive stimuli arising from the operative site. It minimizes the rise in blood sugar, cortisol, catecholamines, rennin and aldosterone release associated with stress. Postoperative negative nitrogen balance and secretion of antidiuretic hormone are inhibited.

Hepatic and Renal Effects

The hepatic blood flow decreases and is directly proportional to the decrease in blood pressure. There may be more of hepatic oxygen extraction. Renal blood flow is maintained by autoregulation and does not decrease till mean arterial pressure go below 50 mmHg.

Thermoregulation and Shivering

Hypothermia results from heat loss to the cold environment due to vasodilatation.

Genitourinary Systems

Sphincters of bladder are not relaxed, and tones of ureters are not greatly altered. Penis is often engorged and flaccid due to paralysis of nerve-erigentes (S2, 3). Postspinal retention of urine may be moderately prolonged as L2 and L3 contain small automatic fibres and their paralysis lasts longer than that of the larger sensory and motor fibres. Uterine tone is unchanged in pregnancy. In the absence of hypotension, spinal anaesthesia has got no effect on the progress of labour and uterine blood flow.

Gastrointestinal Effects

Preganglionic fibresfrom T_5 to L_4 are inhibitory to gut. So in sympathetic blockade the small intestine contracts with relaxed sphincters and peristalsis remain normal. Handling of viscera causes discomfort and bradycardia since vagus is not blocked.

HISTORY OF PAIN

An anesthesiologist has a role to relive pain due to various causes including post-operativepain. Pain – The word derived from a Greek word “poine’ which means penalty. Pain is defined as an unpleasant sensory and emotional experience which is associated with actual tissue damage or potential tissue damage or at leastdescribed in terms of such damage. Aristotle – Described that the pain was an emotion emanating from the heart. Galen - Correctly observed brain was required to manifest the pain and he also proposed that sensation is a property of nervous tissue.

The idea of specific neural pathways for painful sensations began with CHARLES BELL (1774-1842) and FRANCOIS MAGENDIE (1783-1855) who both demonstrated that dorsal roots of the spinal cord transmit sensory information and the ventral root transmit the motor information. In 1948 Ahlquist proposed the designations of α and β receptors. Since then various subtypes of these two main classes have been characterized. Various theories regarding pain transmission including gate control theory (1965) by Melzack and Wall. Endogenous opioids are located at diverse sites in the pain pathway, including dorsal horn of spinal cord which influencesthe rostral transmission of Pain. By using intrathecal or epidural injection, the nociceptive transmission at the 1^{st}synptic relay in the spinal cord may be manipulated.

PHYSIOLOGY OF LABOUR PAIN

UTERINE AND CERVICAL PAIN

The afferent nerve fibres that pass from the uterus and the cervix are somatic sensory fibres which travel via the sympathetic nerves supply of the uterus. These fibres pass through the paracervical tissue along the uterine artery, and then through the inferior, middle and superior hypogastric plexus to the sympathetic chain. These impulses then enter the spinal cord through the 10, 11 and 12^{th} thoracic nerves.

PERINEAL PAIN

Impulses arising from the vagina, vulva and perineum travel in a different pathway. Sensory innervation of this area is through the pudental nerve which enters the central nervous system via 2, 3, 4 sacral nerves.

CENTRAL NERVOUS SYSTEM (CNS)

Upon entering the CNS, these impulses undergo modulating in the posterior horn of the spinal cord. Many neurotransmitters mainly enkephalin, endorphins, serotonin, γaminobutyric acid (GABA), dopamine and epinephrine all participate in the process of conduction of pain impulses and play a role in whether a painful stimulus will ultimately produce the sensation of pain. Obviously applying either of these neurotransmitters or analogues thereof (i.e. Opiate drugs) to the spinal cord or brain can also affect the transmission of pain within the CNS. It is this realization that forms the physiological and pharmacological basis for the application of narcotics within the spinal canal to produce analgesia.

If the synaptic modulations in the dorsal horn permits upward transmission of the stimulus, it will travel upward primarily via the neo and palaeo-spinothalamic tracts.

These impulses can then stimulates the reticular formation and segmental tract in the brain stem and then continue upward to the ventral posterolateralnucleus of the thalamus. From here, fibres project to the sensory cortex for localization and discrimination of pain. Adequate obstetric analgesia not only reduces the physiological or subjective component of pain but may also be beneficial in preventing undesirable reflex effects. The administration of opiates to produce analgesia either for labour or following caesarean delivery has long been an useful technique by which analgesia can be reliably produced. A number of methods (intramuscular, intravenous, continuous intravenous infusion, patient controlled analgesia etc.,) have been successfully used to produce analgesia.

PHYSIOLOGICAL CHANGES DURING PREGNANCY

BODY CONSTITUENTS

Intravascular fluid volume	+35%
Plasma	+ 45%
RBC	+ 20%

CARDIO VASCULAR FUNCTION

Cardiac output	+40%
Stroke volume	+30%
Heart rate	+15%

PERIPHERAL CIRCULATION

Systolic	:	No changes
Systemic vascular resistance	:	-15
Diastolic	:	-15
Central Venous pressure	:	No change
Femoral venous pressure	:	+15

RESPIRATORY FUNCTION

Average changes from non pregnant value

Minute ventilation	:	+ 50%
Tidal volume	:	+ 40%
Breathing Rate	:	+ 10
PaO_2	:	+ 10 mm Hg
$PaCO_2$	:	- 10 mm Hg
pH	:	No change
Total lung capacity	:	No change

Vital capacity	:	No change
FRC	:	- 20%
Expiratory Reserve volume	:	-20%
Residual Volume	:	-20%
Airway resistance	:	-35%
Oxygen consumption	:	+20%
BMR	:	+ 15 -20%

PHYSIOLOGICAL CHANGES DURING PREGNANCY

Body constituents

Blood volume begins to increase in the first trimester and reaches 50% above the non pregnant level in the third trimester. The red blood cell mass also-rises steadily but relatively less than total blood volume with a consequent reduction in hemoglobin concentration deposits a raised total hemoglobin content.

CARDIOVASCULAR FUNCTION

Cardiac output, myocardial contractility, heart rate and stroke volume are increased. The increase in cardiac output starts in the first trimester. Arteriovenous oxygen content difference is reduced until the final month. Systematic vascular resistance is decreased. No change occurs in pulmonary arterial pressure during pregnancy. Blocking the autonomic nervous system may result in dramatic decrease in systematic arterial pressure during pregnancy, suggesting a chronically active sympathetic tone.

RESPIRATORY FUNCTION

Respiratory tract is oedematous due to capillary engorgement. Functional residual capacity is decreased. Although the enlarging uterus causes elevation of diaphragm, total lung capacity and vital capacity remain unchanged due to compensatory increase in the antero-posterior and transverse diameters of chest. The minute volume increases in late pregnancy due to increase in tidal volume and respiratory rate with an increase in oxygen consumption.

RENAL FUNCTION

Changes in renal function are mainly due to increased levels of ACTH. ADH, aldosterone, cortisol and thyroid hormone. Glomerular filtration rate starts increasing early and remains at about 40% above non-pregnant levels by mid pregnancy. Renal plasma flow also increases as much as 50 percent and peaks by the end of the second trimester, remaining high until term.

GASTRO INTESTINAL FUNCTION

Gastro intestinal motility decreases due to a direct effect of progesterone and also by an inhibitory effect of progesterone on plasma motilin. The lower oesophageal sphincter tone is diminished.

HEPATIC FUNCTION

There are no grass morphological changes but functional changes are present in the liver. The plasma cholinesterase level is decreased significantly as early as the first trimester and remains low until delivery.

COAGULATION AND FIBRINOLYTIC FUNCTIONS

Plasma levels of factors VII, X, XII and fibrinogen increase during pregnancy, leading to a hyper coagulable state.

EVALUATION OF THE NEONATE

The importance of assessment of neonate immediately after birth is to promptly treat the depressed infants, who require active resuscitation. As a guide to identify and to treat the depressed neonate, Apgar score is used.

APGAR SCORE

Virginia Apgar of New York City described a system whereby the condition of a neonate can be assessed at one minute and 5 minutes after delivery. The Apgar score has been shown to correlate well with acid-base measurements performed immediately after birth.

EVALUATION OF NEWBORN INFANT USING APGAR SCORE

Sl.No.	Signs	Scores		
		0	1	2
1	Heart rate	Absent	<100/mt.	> 100/mt
2	Respiratory effort	Absent	Slow, irregular	Crying
3	Reflex irritability	No response	Grimace	Cry
4	Muscle tone	Limp	Hypotonia	Active
5	Color	Pale, cyanotic	Body pink; extremities cyanotic	Pink

TIME FOR SUSTAINED RESPIRATION

The time interval between delivery and the establishment of sustained respiration has been used to identify the depressed neonate. A time for sustained respiration greater than 90 sec. indicates a depressed neonate and correlates with Apgar score of 6 or less.

NEUROBEHAVIOURAL TESTING

Neurobehavioural testing is able to detect subtle or delayed effects of drugs administered during labour and delivery that are not appreciated by Apgar score. The testing evaluates neonate's state of wakefulness, reflex (moro, rooting & sucking reflexes) response, muscle tone.

PHARMACOLOGY OF DRUGS

Pharmacology of Bupivacaine

Bupivacaine is an amide linked local anesthetic. It is hydrochloride salt of d (1)-1 butyl 2' 6' pipecoloxylidide and is presented as a racemic mixture.

- ❖ It was synthesized by BO of Ekenstem
- ❖ First reports of its use were published in 1963 by Telivuo.
- ❖ It is derived from mepivacaine and is a very stable compound and may be autoclaved repeatedly.

pKa is 8.2 Partition co-efficient is 27.5

Molecular weight is 288 Protein binding is 96%

Availability

Ampoules : 0.5% bupivacaine hydrochloride 4 ml

0.5% bupivacaine hydrochloride with dextrose (heavy) 4 ml

Vials : 0.25%, 0.5% bupivacaine hydrochloride20 ml.

Dosage

Maximal dose	2 mg / kg body weight
Uses	Spinal
	Epidural
	Caudal
	Continuous epidural
	Peripheral nerve block

ONSET TIME AND DURATION OF ACTION

Site of action	Onset (minutes)	duration (minutes)
Intrathecal	5	180-240
Epidural	15-20	165-225
Branchial plexus	15-20	600

PHARMACOKINETICS

Once rejected intrathecally, it gets absorbed by the nerve rootlets and results in the desired effect. It is rapidly absorbed from the site of injection, but the rate of absorption depends on the vascularity at the site and presence of vasoconstrictors. High lipid solubility of bupivacaine makes it easy for nerve and vascular tissue penetration. 80-95% of the absorbed bupivacaine binds to the plasma protein.

DISTRIBUTION

Rapid distribution phase (α)

In this phase the drug is distributed to highly vascular region, t ½ α being 2.7 mts.

Slow disappearance phase (β)

In this phase the drug distributes to slowly equilibrating tissues, t ½ β being 28 mts.

Bio-transformation and excretion phase (δ)

t ½ δ is 3.5 hours. Clearance is 0.47 litres / minutes.

Bio-transformation

It is by the liver. The N-dealkylated metabolite is pipecolyloxylidine.

Excretion

It is through the kidney.

4-10% of the drug is excreted unchanged in urine.

Mode of Action

a. Site of Action

1. The spinal nerve rootlet-fine nerve filaments having a large surface area are exposed to the local anesthetic.
2. Posterior and lateral aspects of the spinal cord itself.

Sodium channel blockade

They impede sodium ion access to the axon-interior by occluding the transmembrane sodium channels thus denying the process of depolarization and axon remains polarized. It is a non-depolarization block.

Pharmacodynamics

It has got a longer duration of action but a slower onset.

Cardiovascular system

It reduces cardiac output by reducing the sympathetic tone, by slowing the heart and by reducing the venous return. It produces a fall in arterial blood pressure but it is relatively slow and is seldom very profound. It produces a fall in central venous pressure. It causes an increase in lower limb blood flow. It causes a reduction in incidence of deep vein thrombosis.

Respiratory System

Spinal blockade seldom, if ever causes respiratory problems.

Gastro Intestinal Tract

There is an increase in gastro intestinal motility and emptying of gastric contents is better.

Toxicity

Toxicity is related to plasma level of unbound drug and more likely due to an inadvertent intravenous injection. Systemic toxicity-reactions primarily involve central nervous system and cardio vascular system. The blood level required to produce central nervous system toxicity is less than that required to produce circulatory collapse.

Central Nervous System Toxicity

Initial symptoms include feeling of light headedness and dizziness, followed by visual and auditory disturbances. Objective signs are excitatory and include shivering, muscle twitching and tremors. Ultimately generalized tonic, clonic seizures occur.

CARDIO VASCULAR SYSTEM TOXICITY

The rate of depolarization in fast conducting tissue of purkinjefibres and ventricular muscle is decreased. The rate of recovery of bupivacaine induced block is slower than that of lignocaine. Extremely high concentration of the drug causes sinus bradycardia and cardiac arrest.

Renantiomer is more toxic than S enantiomer.

Pharmacology of Fentanyl

Fentanyl is the only opioid available for various forms of administration. It can be used by the following routes.

- Intramuscular
- Intravenous
- Neuraxial – Spinal, epidural administration for intra and postoperative analgesia.
- Transdermal-applied before the induction of anaesthesia and left in place for 24 hours. It can reduce the amount of parental opioid requirements for post-operative analgesia.
- Transmucosal – to decrease the anxiety and to facilitate induction of anaesthesia especially in children.
- **Dosage**

Intramuscular	:	50-100μg (1-2 μg/kg)
Intravenous	:	50-100μg (1-2 μg/kg)
Intrathecal	:	10-25μg (0.25μg/kg -0.5μg/kg)
Epidural	:	Bolusdose 1μg/kg
Continuous infusion	:	30-100μg/hr.
after the bolus		

Onset time and duration of action

Routes of administration	Onset time (mins)	Duration of action (hrs)
Im	7-8	1-2
Iv	Immediate	0.5-1
Epidural	10	2-3

Pharmacokinetics

Molecular weight	:	528
pKa	:	8.4
Plasma protein binding	:	84%
t ½ α	:	1-2 mins.
t ½ β	:	10-30 mins.
t ½ γ	:	2-4 mins.

Being a highly lipophilic opioid the vascular uptake and rapid circulation to brainstem is more and the rostral spread is of smaller magnitude. This kinetics of fentanyl is in contradiction to morphine and clinically produces rapid onset, shorter duration of action, early but not delayed respiratory depression. Once the fentanyl is systematically absorbed it is rapidly redistributed to inactive tissue sites such as fat and skeletal muscles with an associated decline in plasma concentration. The lungs also serve as a large inactive storage site, with an estimate 75% of the initial fentanyl dose undergoing first pass pulmonary uptake. Fentanyl is extensively metabolized by dealkylation, hydroxylation and amide hydrolysis to inactive metabolites, including norfentanyl and desprionylnorfentanyl that are excreted in the bile and urine.

The pharmacokinetics of fentanyl can be described as three compartmental models with a distribution time of 1.7 minutes, redistribution of 13 minutes and a terminal half time of 219 minutes. The volume of distribution is 4 L/kg.Gastric acidity can ionize fentanyl and prevents its systematic absorption and once the acidity is neutralized, the systemic absorption can increase the plasma fentanyl concentration. Enterohepatic circulation of fentanyl can explain the delayed respiratory depression seen in some cases.

MODE OF ACTION

Opioid Receptors

Mu, Kappa, Sigma, Delta and Epsilon are the opioid, receptors distributed in the supraspinal areas (periaqueductal grey matter, caudate, striatum and putamen) and the spinal cord (throughout the spinal gray matter with the highest density in the substantia gelatinosa).Fentanyl acts on the mu receptors in the supraspinal areas and on kappa and delta receptors in the spinal cord producing spinal analgesia.

Intrathecally administered fentanyl gets attached to the spinal opioid receptors situated densely in the substantia gelatinosa and systemic absorption of the fentanyl can lead to supraspinal receptor binding and its effects. Investigations suggest that different receptors are existing for different opioids. These receptors are distributed throughout the CNS and other parts of brain like paleothalamic pathway, limbic system, medial thalamic, nuclei, periaqueductal grey matter, reticular formation, periventricular areas of medulla, substantia gelatinosa of spinal cord, lamina I & V of spinal cord. Opiate receptors are proteolipids which can bind to both agonists & antagonists.

Classification

μ-receptor

Stimulation of this receptor causes supraspinal analgesia, euphoria, respiratory depression and physical dependence. This receptor is stereospecific and naloxone sensitive, Endogenous ligand for μ receptor is endorphin and exogenous ligand is morphine, the selective antagonist being naloxone.

μ_1-receptor

Stimulation of this receptor causes supraspinal analgesia and physical dependence.

μ_2-receptor

Stimulation of this receptor causes respiratory depression, inhibition of gastro intestinal tract motility and cardiovascular system effects.

K-Receptor

Ketocyclozocine is the prototype agonist. Stimulation causes, spinal analgesia, sedation, miosis, physical dependence and inhibition of ADH secretion. Endogenous ligand is dynorphin and the selective antagonist is naloxone.

δ-receptor

This receptor has high affinity for adrenocorticotrophic peptide hormone. Function is not clear but it may be responsible for modulation of activity of μ receptors. It may cause spinal analgesia and can cause respiratory depression it is not sterospecific and is naloxone insensitive. The protype agonist is d-Ala-d leuenkephalin.

α-receptors

Stimulation of this receptor causesdysphoria, hallucination, mydriasis and respiratory depression.

ε-receptors

This receptor is not well characterized at present and it may be responsible for the stress response to pain. Endogenous ligand is β – endorphin and the antagonist being naloxone. Opioid receptors in the limbic system and hypothalamus are related to the emotional components of pain. Encephalin-containing receptors are found in Meissner's plexus of duodenum, which probably affects gastro-intestinal motility. Opiate receptors are found in large numbers in the area postrema, which contains chemoreceptor trigger zone-the site where opiods are thought to induce nausea and vomiting.

Mechanism and site of action

Recent studies now point to the dorsal horn of spinal cord as the site of action of spinal opiate based upon ionatophoretic and micro-injection data. Radiolabelled morphine or fentanyl showed a strong focus of activity on the substantia gelatinosa. Opiate receptors are located both pre-synaptically at the terminal of primary sensory afferents entering the dorsal horn and on the dentrites of post-synaptic membranes. Pre-synaptically, opiate peptides inhibit the release of substance-P, glutamate and other neurotransmitters like acetylcholine, noradrenaline, dopamine from sensory neurons.

They also act post-synaptically by decreasing the excitatory, post-synaptic potentials induced by persistent afferent stimulation. Intraoperative subarachnoid narcotics potentiate the antinociception provided by the local anesthetic agent.

There is enhancement of comfort and also the visceral manipulations are better tolerated. Fentanyl also binds to M_3muscarnic receptors in the heart leading to bradycardia which can be prevented by giving atrophine to the patient. Fentanyl also antagonizes 5 hydroxytryptaminelevel in the brain thereby potentiating the analgesic activity of other opioids.

PHARMACODYNAMICS OF FENTANYL

Cardio Vascular System

It produces bradycardia by binding to M3 receptors. It slows AV node conduction and prolongs PR interval.

Respiratory System

It can cause early respiratory depression. Peak effect is noted 5 to 15 minutes following intravenous injection. Very rarely delayed respiratory depression can occur.

Musculo Skeletal system

It may cause muscle rigidity, particularly involving the muscles of the chest wall. Skeletal muscle movements of various groups in the extremities of neck and extra ocular muscles have been reported during induction of anesthesia. This effect is related to the dose and speed of injection.

Central Nervous System

It produces euphoria: sedation and miosis. It will not interfere with evoked potential monitoring.

Gastrointestinal Tract

It causes nausea, vomiting and biliary spasm.

ADVERSE EFFECTS

Respiratory Depression

Various studies have showed that respiratory depression may occur after any opioid irrespective of its route of administration.

Urinary retention

It is likely to interact with opioid receptors located in sacral segments of spinal cord. This in turn promotes inhibition of sacral parasympathetic nervous system outflow which causes detrusor muscle relaxation and an increase in maximum bladder capacity leading to urinary retention.

Pruritus

Most common side effect is pruritus. The incidence is 0-100%. It may be generalized or localized to the face, neck and upper thorax. The sensation appears around or just after the development of analgesia by epidural or intrathecal opioids.

Nausea and Vomiting

Intraoperative incidence is 30%. It may be due to the cephalad migration of drug and subsequent interaction with opioid receptors in vascularized area postrema.

Hypertension

Intrathecal pethidine and sufentanil cause hypotension whereas intrathecal fentanyl does not cause this effect. The mechanism is not known.

Delayed gastric emptying

This effect is mediated at the spinal level and hence neuraxial opioids are not exempt from this effect.

Other effects

Chest wall rigidity

Apnoea

Bradycardia

Diaphoresis

Emesis

Dizziness

Blurred Vision

Over dosage and treatment

The manifestations of fentanyl overdosage are an extension of its pharmacological actions.

Effects	Treatment
Hypoventilation	Oxygen therapy
Assisted or controlled ventilation	
Severe respiratory depression	Naloxone
Hypotension	Paraenteral fluid therapy
Pruritus	Chlorpheneramine

Clonidine

Pharmacology of Clonidine

It is a 2, 6 – dichloro phenyl-4, 5 dihydro, 1H-imidazol-2, amine with formula $C_9H_9Cl_2N_3$. It is an imidazoline derivative and acts on both α_1 and α_2 receptors with ratio of α_2 and α_1 are 220:1. It stimulatesα_2 receptors both at central and peripheral sites. It is not a pure α_2 agonist and it also acts on non-adrenergic imidazoline preferring receptors.

Availability

Ampoule – 1ml containing 150 μgm

Various routes of administration and dosage

Route	Dose
Intra Nasal	2-4μg/kg
Oral	4 – 5 μg/kg
Intravenous	Bolus : 1-2μg/kg Infusion: 0.18-3.16μg
Rectal	2.5-5 μg/kg with atropine 50μg/kg
Caudal	1-2μg/kg
Spinal adjuvant	1-2 μg/kg
Epidural adjuvant	0.0625% bupivacaine with fentanyl 1 μg/ml and clonidine 0.6μ/ml at a rate of 0.2 ml/kg/hr.
Sciatic nerve block	0.2% ropivacaine 0.4 mg/kg/hr with clonidine 0.12 μg/kg/hr as infusion
Para verterbral block	19 ml bupivacine as a bolus with Clonidine 150 μg/kg given every 48 hours for 3 weeks via catheter.

Pharmacokinetics

Absorption

It is well absorbed by all the routes-oral, intravenous, intramuscular, transdermal etc. The bioavailability is nearly 100% by oral route. Elimination half-life of 6 to 12 hours with the mean of 12 hours, about half the drug administered is excreted unchanged through urine and the half-life of the drug is increased with renal failure.

Metabolism

Fifty percent of the drug is metabolized in the liver to inactive metabolites which are excreated in the urine.

Drug Interactions

Tricyclic antidepresents and presumably phenothiazines and butyrophenone interfere with the action of Clonidine, but butyrophenone administration may produce hypertensive crisis at least theoretically, even though none has been reported. Acute Clonidine administration reduces anesthetic requirements by 40 to 60% chronic administration reduces by 10 to 20%.

Sub types of α_2 receptors

1) α_{2A} 2) α_{2B} and 3) α_{2C}

α_{2A} - mediates sedation, sympatholysis, analgesia

α_{2B} – vasoconstriction, anti-shivering mechanism

α_{2C}–Sturtle response. It is the response of the body and minds to sudden unexpected stimuli e.g. a flash of light.

Mechanistic Information

α_2 receptors are located on primary afferent terminals (both peripheral and spinal endings) on neurons in superficial laminae of the spinal cord and within the brainsterm nuclei implicated in analgesia, supporting and possibility of analgesic action at periphery, spinal and brainsterm sites. Notably the axons of peripheral nerves or lacking the α_2 receptors, but Clonidine produces minor degree of conduction blockade at higher concentration with some preference to 'C' fibers.

This action may underlie in part, in the enhancement of peripheral nerve block when this agent added to the local anesthetics. Analgesia produced by intrathecal Clonidine in not produced by systemic absorption because the peak levels in arterial blood is achieved within 10 minutes and in intravenous blood is within 30 to 45 minutes,Elimination from the blood is slow and the duration of analgesia is relatively brief and this point is contradicting against an action by systemic absorption and redistribution to central and peripheral site.

Acetylcholine and Neuraxial Clonidine:

Epidurally administered Clonidine produces increase in release of acetylcholine in the dorsal horn of the spinal cord, but not in the ventral horn. Analgesia produced by the epidural Clonidine in volunteers is enhanced by the intrathecal injection of choline-esterase inhibitor neostigmine.

This interaction is additive only in humans, but synergistic in animals. This supports the cholinergic mechanism in spinal analgesia produced by the Clonidine. The descending nor-adrenergic pathways release nor-adrenaline to cause analgesia directly and by stimulating the release of acetylcholine.

Clonidine and local anesthetics

Clonidine enhances both sensory and motor blockade by three possible mechanisms.

1. Clonidine blocks the conduction in the 'C' fibers and in the "Aδ" fibers, and increases the K^+ion conductance in isolated neurons in-vitro and it intensifies the conduction blockade produced by the local anesthetics, because the systemic pharmacokinetics are not the factor in vitro experiments. These data supports the direct effect of the Clonidine on neural transmission in high local concentration.

2. Clonidine may produce vasoconstriction and thereby inhibiting the removal of the local anesthetics surrounding the neural tissues, but this occurs only in high concentrations and there is little evidence for this mechanism with clinically used concentrations and this is confirmed by the observation that the plasma lignocaine concentrations is same with or without Clonidine addition, but this plasma lignocaine concentrations is reduced because of decreased systemic absorption.

Pharmacodynamics effects:

Action of the clonidine on myocardial performance

1) Produces bradycardia partly due to vagomimetic action and partly due to pre-synaptically mediated inhibition of nor-adrenaline release at neuroreceptor junction. Although it depresses the AV nodal conduction, severe bradyarrythmias are rare with Clonidine.
2) It increases the cardiac output by reducing the afterload, but in some patients, it reduces cardiac output due to the decrease in the heart rate.
3) It reduces the Oxygen demand and has been shown to reduce the infarct size when administered to the patients in the acute phase of myocardial infarction. Haemodynamic effects after neuraxial administration starts within 30 minutes and reaches the maximum effect within 1 to 2 hours and lasts for approximately 6 to 8 hours after single injection. Delayed onset of hypotension has not been observed with the use of Clonidine for analgesia alone or in combination.

This combination produces higher degree of sympatholysis and the combination of Clonidine and local anesthetics in neuraxial route and resulting hypotension is also high. Clonidine has minor or no effects on responses to vasoconstrictors or atropine given to treat hypotension or bradycardia that may occur with neuraxial anaesthesia.

Clonidine pre-treatment delays the central nervous system or cardiovascular system toxic manifestations of Bupivacaine overdose and also it improves ventricular electrophysiologic parameters in dogs. But this is not to imply that Clonidine should be used as treatment for Bupivacaine overdose, but rather to emphasize that, should such overdose occur, inclusion of Clonidine is unlikely to exacerbate the problem. Spinal neostigmine counteracts the hypotension induced by Clonidine due to cholinergicallymediated increase in pre-ganglionic sympathetic neuron activity and it also enhances analgesia produced by Clonidine. This combination may be useful clinically.

Sedation:

It commonly occurs after neuraxial administration of the Clonidine. After epidural administration, Clonidine by its systemic absorption and vascular redistribution to higher centers produces sedation.

Site of Action

The brain stem nuclei called as locus ceruleus which is involved regulation of sleep, wakefulness. It is inhibited by P Protein mediated mechanism that involves inhibition of adenyl cyclase.

Dose Dependent Sedation:

Regardless of route administration the Clonidine produces rapid sedation in less than 20 minutes over the dose range of 50-900 μg. After a large epidural bolus dose (700 μg) sedation is intense for 4-6 hours and reduced the need for other sedatives, anxiolytics when Clonidine given intraoperatively.

Unique feature of sedation

The Clonidine produces arousable sedation but with other drugs which acting on GABA receptor it alsoproduces clouding of consciousness and causes paradoxical agitation.

Respiratory Depression:

Although the respiratory depression produced by narcotics may be due to noradrenergic mechanism which is supported by some evidence. Clonidine alone does not induce respiratory depression even with massive dosesand it does not potentiate the depression produced by narcotics. Occasional reports of upper airway obstruction during deep sedation with Clonidine and which is accompanied by transient fall in oxygen saturation. So that monitoring the patients with pulse-oxymetry may be needed for 30 minutes to 2 hours after large bolus doses.

Hormonal effects:

As it is a potent sympatholytic agent, it reduces but not suppresses the stress hormones like nor-adrenaline, adrenaline, ACTH and cortisol. It promotes the release of growth hormone, but the effect is short lived. This also reduces the insulin release by direct action on islet cells, but it is clinically insignificant.

Mechanism of Antishivering effect:

The clonidine synchronously decreases the cold-response threshold while slightly increasing the sweating threshold and thus suggesting that it acts on central thermal regulatory system rather than preventing shivering peripherally.

Urinary retention and Clonidine

Intrathecal opioids may produce urinary retention. Clonidine persedo not produce any urinary retention and it may actually hastens the time to first micturition after spinal anesthesia.

Parasympathetic system and Clonidine

Clonidine produces bradycardia, AV nodal conduction delay. Vasoconstriction and anti-shivering mechanism is due to the direct action on postsynaptic α_2 receptors present in the vascular smooth muscle.

Uses

1. It is used for pre-anesthetic medication
2. It helps to reduce the stress response
3. It helps to treat the withdrawal symptoms of alcohol, narcotics, and tobacco as it reduces the sympathetic manifestations of withdrawal syndrome.
4. It is used to treat the post-menopausal hot flushes.
5. It helps to differentiate the pheochromocytoma and hypertension.
6. It helps to treat both intra-operative and postoperative shivering
7. It helps to treat the postural hypotension as it has direct action on vascular smooth muscle.

Side Effects

1. Excessive sedation in higher doses produces upper airway obstruction and decrease in oxygen saturation.
2. Dryness of the mouth
3. Contact dermatitis if it is used as a transdermal patch.
4. Sexual dysfunction
5. Abrupt-withdrawal in hypertensive patients leads to hypertensive crisis.

HISTORY AND REVIEW OF LITERATURE

History

Subarachnoid Block

In 1885, J. Leonard Corning, a New York neurologist first used cocaine experimentally dogs. In man, the first spinal anaesthesia was conducted by August Bier on 16.08.1898 with cocaine 3 ml as 0.5% solution. It was followed by Rudolf Matasin America and Tuffier in France.

Bupivacaine

Bupivacaine was synthesized in Sweden by Ekenstam and his colleagues in 1957 and used clinically by L.J. Telivuo in 1963.

Intrathecal Opioids

Gate control theory of pain (1965) by Melzack and Wall focused the attention on importance of dorsal horn of spinal cord in the modulation of pain. In 1973, Pert &Sndyer identified the specific opiate receptors in the substancia gelatinosa of dorsal horn of spinal cord. In 1976, spinal effects of intrathecal opiates in animals were demonstrated by Yaksh& Rudy. In 1977, Wang, Naurs& Thomas studied the effect of intrathecal morphine in men in intractable pain of lower limb due to malignancies invading lumbosacral plexus.

In 1980, Davier et al, identified that respiratory depression with intrathecal morphine was reversed with systemic naloxone, without reversing analgesia. In 1981, Yaksh& Rudy described the action of intrathecal pethidine and morphine in primates by ionotophoretic administration of the drugs into the substantia gelatinosa.

They found out high level of opiate binding in substantia gelatinosa indicating the presynaptic action of opiate. Spinal opiates also seemed to cause significant elevation of nociceptive threshold.

In 1984, Huang HJ, Ishimain T, Yambe studied the use of intrathecal morphine for postoperative pain relief. In 1988, Inagaki Y, Takeyama E studied the efficacy of postoperative pain relief after the use of intrathecal buprenorphine with local anesthetic agent and found it to prolong the postoperative analgesia.

Intrathecal Clonidine

Bonnet et al., studied that spinal Clonidine as an adjuvant with Bupivacaine in orthopedic surgeries and proved that the combination was effective in preventing the tourniquet pain and effectively prolonging the post-op analgesia.

Fogarty et al compared Clonidine vs. morphine with Bupivacaine in patients undergoing total hip replacement surgeries. Intrathecal Clonidine prolonged the duration of spinal analgesia, but was markedly inferior to the intrathecal morphine in providing subsequent postoperative analgesia.

Grace et al studied the co administration of Pethidine with Clonidine in spinal anaesthesia for total hip replacement surgeries.

Monica brunschwiller et al compared intraoperative anesthetic and haemodynamic effects of clonidine-bupivacaine, morphine-bupivacaine and placebo-bupivacaine combinations during continuous spinal anaesthesia in knee replacement surgeries and concluded that 0.15 mcg Clonidine but not 0.15 mg morphine prolonged surgical analgesia when added to 10 mg plain Bupivacaine.

Pan etal studied the analgesic effects of intrathecal neostigiminevs. Clonidine with Bupivacaine in cesarean section. Their study showed that the combination of 150 μg Clonidine and 50μg neostigmine provided longer post-surgical analgesia than with either drug used alone. However, this combination also produced significantly more adverse effects of prolonged motor blockade nauseaand vomiting.

Philip.J.Siddall et al studied that the efficacy of intrathecal Morphine and Clonidine in the treatment of pain after spinal cord injury. They demonstrated that administration of a combination of morphine and Clonidine into the spinal fluid can provide substantial pain relief in some people with this type of pain.

Spinal Opioids and Labor analgesia

Opiates have been used as analgesic agents in obstetrics since the Babylonions discovered their pain relieving properties. Subarachnoid block was first used for obstetric delivery in 1901 by Kresis in Germany.

Intrathecal pethidine in labour and delivery was reported in-British Journal of Anaesthesia in 1987.Morphine was the first opioid to be used intrathecally but has limitations of long latency, high incidence of maternal side effects, poor perineal analgesia (Alper M, Intrathecal morphine; a new method of obstetric analgesia, Anaesthesiology, 1979: 51:378-379).

Fentanyl and Intrathecal anaesthesia

The increased availability of lipid soluble with shorter latency and demonstration of synergistic effect of opioids when combined with local anesthetic have led to the widespread use of neuraxial opioids in labour. The effect of lipophilic agents are better when administered at the level at which analgesia is required. Commonly used opioids are meperidine, fentanyl and sufentanil.

(Honet JE, Arkoosh VA, Norris MC et al., comparison among intrathecal fentanyl, meperidine and sufentanyl for labour analgesia Anae Anal 1992; 75:734-739).

Justins et al., 1982: The doses of local anesthetic required for labour pain relief can be diminished to one half to one thirds with the addition of intrathecal opioids and provide excellent analgesia for the entirety of labour. Mok et al, 1984; Intrathecal injection of fentanyl, sufentanil, alfentanil and nalbuphine have been reported for post-operative analgesia with promising results.

Belzarene, Sergio D. et al 1990: The clinical effects of fentanyl administered into the subarachnoid space were assessed in 120 caesarean sections with spinal anaesthesia using 0.5% hyperbaric bupivacaine. They concluded that regression of anaesthesia to the T_{12} dermatome took a longer time as the dose of fentanyl was increased.

Neonatal status was not depressed

Wang, Chen MB et al., 1993: This study examined the effects of bupicacaine administered intrathecally on sympathetic efferent and 'A-Delta' and 'C' fibre-mediated afferent pathways in dogs and the interactions with intrathecal fentanyl. The results showed that intrathecal bupicacaine has not selectivity for the afferent and efferent pathways and intrathecal fentanyl acts synergistically to enhance the effect of bupivacaine on the afferent pathway without a measurable effect on sympathetic outflow.

Singh, Harbhej, Yang et al 1995; they studied the effect of intrathecal fentanyl on the onset and duration of hyperbaric bupivacaine-induced spinal block in adult male patients undergoing genitourinary surgery. They concluded that fentanyl 25μg, prolonged the duration of bupivacaine-induced sensory block (sensory regression to L_1 dermatome) by 28% and increased the postoperative analgesia.

Hunt et al, reported that the addition of fentanyl 6.5μg to hyperbaric bupivacaine reduced the intraoperative opioid requirement in patients undergoing caesarean delivery under spinal block. Belzarena et al demonstrated that low dose fentanyl 0.25μg/kg with bupivacaine 0.5% provided excellent surgical anaesthesia with few side effects. An increased dose of fentanyl to 0.5μg/kg was associated with an increased incidence of adverse effects in patients undergoing caesarean delivery. Palmer CM et al., 1995: 15μg of fentanyl was added as a sole adjuvant to hyperbaric lidocaine in spinal anaesthesia in parturients undergoing caesarean delivery and concluded that the addition of fentanyl increases the duration of effective analgesia by approximately 30 minutes and provides a protective effect regarding nausea and vomiting in the post operative period.

Dahigren, Gunnar et al 1997, compared the effects of intrathecal sufentanil 2.5 and 5 mg, fentanyl, 10μg, and placebo when administered together with hyperbaric bupivacaine 0.5%, 12.5 mg for caesarean section. This demonstrated that small doses of fentanyl or sufentanil (Synthetic opioids) added to bupivacaine (local anesthetic) for spinal anesthesia for caesarean section reduce the need for intraoperative antiemetic medication and increase the duration of analgesia in the early postoperative period compared with placebo.

Ce-Ben David et al 1997: by exploring the synergism between intrathecal opioids and local anesthetics, it may be possible to augment the spinal anaesthesia without prolonging the recovery. Based on this fact, they have done the study on 50 patients undergoing ambulatory surgical arthroscopy. Implications; Small dose bupivacaine is inadequate for this procedure, but the addition of fentanyl makes it reliable.

Cang FC, Tsai FC et al 1998: Neuraxial opioid may augment the analgesia produced by local anesthetic through direct binding with the spinal opioid receptors. Theoretically, the reduction of local anesthetic by addition of fentanyl would provide better haemodynamic stability and good anesthetic status. They conducted the study in 30 healthy parurientsundergoing caesarean section They concluded that the combination of small-dose bupivacaine with fentanyl could provide more stable haemodynamic status, longer post operative analgesia and lower incidence of shivering. The incidence of pruritus was higher but usually mild.

Roussel JR et al, 1999: The have conducted a study on the effects of intrathecal fentanyl on duration of bupivacaine spinal blockade for outpatient knee arthroscopy and concluded that fentanyl does not enhance the onset and duration of sensory or motor block produced by intrathecal bupivacaine. Fentanyl however prolongs post operative analgesia and increases the risk of pruritus.

Sarvela PJ et al 1999: They compared the effect of 9 mg of intrathecal plain and hyperbaric bupivacaine-both with fentanyl-for caesarean delivery.

They concluded that either plain or hyperbaric bupivacaine with fentanyl intrathecally provided similar onset, depth and duration of sensory anesthesia to caesarean delivery with good maternal satisfaction.

Choi DH, Ahn 2000: The study was performed on 120 patients for caesarean delivery. They hypothesized that the addition of fentanyl could reduce the dose of bupivacaine necessary to achieve adequate surgical anaesthesia.

They concluded that the optimal dose of hyperbaric bupivacaine to produce surgical anaesthesia was 12 mg, which was accompanied by high sensory block. With the addition of 10μg of fentanyl, the dose of bupivacaine could be reduced to 8 mg in spinal anaesthesia for caesarean delivery.

Ben-David B, Frankel R et al, 2000: They student the effect of mini dose bupivacaine-fentanyl spinal anaesthesia for surgical repair of hip fracture in the aged.

The synergism between intrathecal opioid and local anesthetics may make it possible to achieve reliable spinal anaesthesia for surgical repair of hip fracture in the aged.

The synergism between intrathecal opioids and local anesthetics may make it possible to achieve reliable spinal anaesthesia with minimal hypotension using a small dose of local anesthetic.

20 patients for more than 70 years of age for surgical repair of hip were divided into 10 patients of 2 groups each.

Group A, received bupivacaine 4 mg + fentanyl 20μgGroup B, received 10 mg bupivacaine

They concluded that the mini dose combination caused dramatically less hypotension than 10 mg bupivacaine and nearly eliminated the need for vasopressor support of blood pressure.

Clonidine and Intrathecal Anesthesia

Dekock.M. et.al, studied spinal clonidine with ropivacaine in ambulatory knee anthroscopy surgeries. They concluded that small-dose intrathecal clonidine (15μg) plus 8 mg intrathecal ropivacaine produces adequate and short-lasting anaesthesia for knee-arthroscopy.

Debrydnjov I et al, have tried 6 mg of 0.5% heavy Bupivacaine with 15μg Vs. 30μg of Clonidine for unilateral spinal anaesthesia in unilateral inguinal hernia surgeries and showed it have produced excellent post-op analgesia. The concluded that use of Clonidine as adjuvant to small dose 6 mg Bupicacaine for ambulatory inguinal herniorraphy.

Michael .J. Peach et. al., (10 (2004) anaes.analg., 2004: 95:56-59) – studied intrathecal fentanyl with morphine and varying doses of Clonidine in cesarean surgeries for post-op analgesia. A multimodal approach to post-cesarean analgesia, using subarachnoid Bupivcaine, fentanyl, morphine 100μg, and Clonidine 60μg, improves pain relief compared with morphine 100μg or Clonidine 150μg alone, but increases intra-operative sedation and may increase peri-operative vomiting.

Alain Rochette et al studied spinal Clonidine in neonates. Spinal anesthesia is suitable but often too short for complete surgery in newborns. This controlled, randomized, prospective, dose-ranging study was conducted in 75 neonates to test the hypothesis that Clonidine could significantly lengthen Bupivacaine spinal block. He concluded that Clonidine 1 μg/kg, added to spinal isobaric Bupivacaine, doubles the duration of the block without significant deleterious hemodynamic or respiratory side effects.

Van Tuiji et al (12. (2006) Br. J. An. 97(3); 365-70) have studied the addition of intrathecal clonidine to hyperbaric Bupivacaine on post-op pain and morphine requirements after cesarean section. They concluded that addition of 75μg Clonidine to hyperbaric Bupivacaine 2.2 ml prolongs spinal analgesia and motor block after cesarean section and improves early analgesia without any clinically relevant maternal or neonatal side effects.

B.S. Senthil, et al., (13 (2007), I.J.A), have studied the efficacy of low dose intrathecal Clonidine as adjuvant to bupivacaine in gynecological surgeries. They have added 1 μg/kg of Clonidine with 2.5 ml of Bupivacaine Vs. plain Bupivacaine. They concluded that by adding clonidine, the postop analgesia is significantly prolonged with an effect on sedation, heart rate and MAP which does not require any therapeutic intervention.

MATERIALS AND METHODS

Following approval by the institutions ethical committee, this prospective study was done at Tirunelveli Medical College Hospital, Tirunelveli in 120 patients undergoing elective or emergency caesarean section after getting informed consent from each patient and explaining the procedure. This is a randomized prospective comparative study.

Inclusion Exclusion Criteria

Term, parturient, ASA I an ASA IE who were fit to undergo spinal anaesthesia for caesarean section, age between 18-35 yrs., are selected. Patients with medical and obstetrical complications and impaired placental function were excluded; patients who were converted to general Anaesthesia were also excluded from the study.

Preoperative Preparation

Preoperatively all patients were seen by the anesthetist. The procedure was explained in detail and informed consent was obtained. No premedication was given. Patients were randomly allocated into 3 groups of 40 each.

A- Control Group - Injection (0.5%) Bupivacaine 1.8 ml + 0.4 ml NS

B- Study group 1 inj. (0.5%) Bupivacaine 1.8 ml + Clonidine 30 μg) + 0.2 ml NS.

C- Study group 2 Inj (0.5%) Bupivacaine 1.8 ml + Clonidine (30 μg) +fentanyl (10μg)

Procedure

- On arrival to operation theatre, basic monitoring was applied to all patients and basic pulse rate, blood pressure, oxygen saturation and respiratory rate were recorded.
- Intravenous line with 18 g canula was established and preload of 250-300 ml of crystalloid was given to all patients.
- Following resuscitative measures were kept ready before the start of the procedure: Boyles machine with oxygen source, laryngoscope and appropriate size blades, suction apparatus, vasopressors (Ephedrine), naloxone and other emergency drugs.
- The subarachnoid block was performed in right lateral position with 23 G spinal needle through L3, 4 space. Free flow of CSF was ensured before introducing the drug. The drug injected was according to the group assigned.

A- Injection (0.5%) Bupivacaine 1.8 ml + 0.4 ml NS

B- inj. (0.5%) Bupivacaine 1.8 ml + Clonidine 30 μg) + 0.2 ml NS.

C-Inj (0.5%) Bupivacaine 1.8 ml + Clonidine (30 μg) + fentanyl (10μg)

Drugs were measured in a sterile tuberculin syringe. Thorough aseptic precautions were taken during the addition of injection and making the final injection.

Immediately after the intrathecal injection the patients were gently turned to supine position with leftward tilt by a wedge under right buttock 100% oxygen was given through Magills breathing system till the delivery of baby.

Assessment of Patient and Recording of Data

Time of subarachnoid block was noted.

Following observations were made

1. Time of onset of analgesia
2. Time of maximum cephalic spread
3. Upper level of sensory block.
4. Grade of motor block obtained according to bromage motor scale.

Bromage motor scale

0- No paralysis

1- Inability to raise extended legs.

2- Inability to flex the knee joint

3- inability to flex the ankle joint

After the establishment of an adequate level of analgesia, the surgeons were allowed to operate and the time of beginning of surgery was noted.

Blood pressure, pulse rate, respiratory rate and Spo_2 were monitored intraoperatively every 2 minutes for the first 10 minutes and every 5 minutes till the end of surgery. Patients were watched for side effects like hypotension, bradycardia, and vomiting, itching and respiratory depression.

Any hypotension (30 % fall from base line) was treated with oxygen, intravenous fluid and inj. ephedrine. Any bradycardia (pulse rate <60 mt) was treated with inj. atropine

Nausea and vomiting were treated with inj. metaclopromide

Pruritis if complained was treated with inj. chlorpheniramine maleate.

Two segment regression time

Time to decrease from maximum sensory level to 2 segments below that level was noted.

Sedation state was assessed by

Brain and Ready sedation score

1. Awake and alert
2. Drowsy
3. Sleepy but easily arousable on call.
4. Sleepy but difficult to arouse.

In the postoperative period, any complications to the mother and baby, especially that is attributed to opioids like respiratory depression, nausea, vomiting, pruritus were noted (one of the expected complication i.e., urinary retention could not be studied as all the patients were invariably catheterized).

Total duration of analgesia was taken as the period from the time of giving subarachnoid block till the patient's first requirement of analgesic medication. Pain was evaluated using 10 cm linear visual analogue scale (VAS) with 0 for no pain and 10 for worst pain. If VAS was more than 6, supplementary analgesia was given and the study was assumed to be concluded at that point.

Foetal Outcome

Immediately after delivery, foetalwell being was assessed by 1 mt. and 5 mt. Apgar score. During the postoperative period, the well being of the baby whether exclusively sedated or not and the nature of cry were noted.

Reflexes like sucking reflex, rooting reflex and moro reflex were tested. Presence of seizures, if any, was also noted. All mothers and their babies were followed up till their discharge.

Statistical Method

Results were expressed as mean $\pm$ standard deviation. Statistical significance was determined by Anova table.

OBSERVATIONS AND RESULTS

Statistical Analysis:

The Randomization of three groups was done by matching their age, height, and weight of their demographic factors and base Physiological factors such as pulse rate, SBP, respiration rate and SPO_2 by ANOVA (Analysis of Variance). The differences between them were interpreted by the Post hoc test of Bonferroni. Similarly, the time for maximum loss of sensation, the 2 segment regression time, pain free time and Apgar score at 1 minute and 5 minutes were compared between groups by ANOVA.

The intra and post-operative pulse rate and SBP at different intervals were compared between groups by ANOVA and interpreted the difference by Post hoc test of Bonferroni.The sensation level and sedation score were analyzed and interpreted by χ^2 test (Chi- square). The above statistical procedures were performed by the statistical package IBM SPSS statistics 20. The P - values less than 0.05 ($P<0.05$) were treated as significant in two tail condition.

Results

Randomization by group matching:

The three groups were namely A (Bupivacaine only), B (Bupivacaine + intrathecal clonidine) and C (Bupivacaine + intrathecal fentanyl + Clonidine). Each group 40 Caesarean Sections were selected and data were collected before during and after surgery. For Randomization the three groups were matched according to their selected and related demographic characteristics and base level Physiological characteristics.

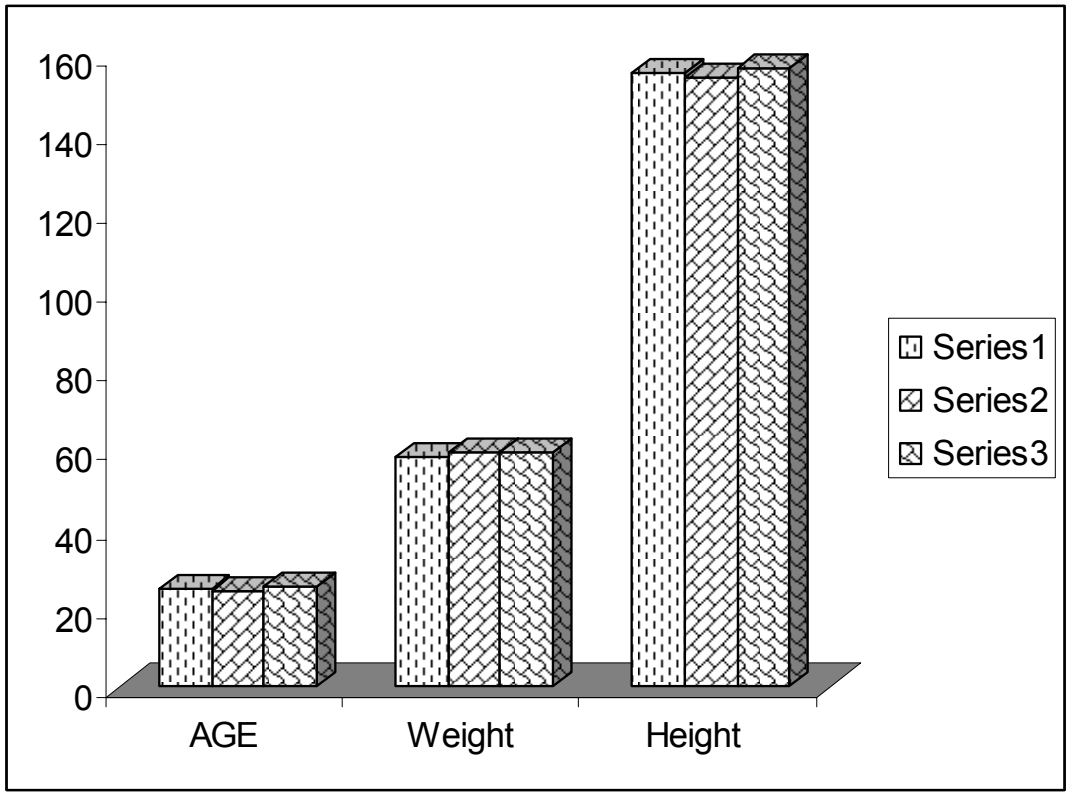


Table-1. Matching of three groups according to their demographic characteristics

Variables	Group	N	Mean	S D	ANOVA 'F'	Df	Significance
Age	A	40	24.6	4.4	1.092	2,117	P>0.05
	B	40	24.1	3.6			
	C	40	25.4	3.8			
Weight	A	40	58.5	5.0	0.319	2,117	P>0.05
	B	40	59.4	8.3			
	C	40	59.6	7.2			
Height	A	40	155.8	6.1	2.021	2,117	P>0.05
	B	40	154.2	4.2			
	C	40	156.8	6.4			

The three groups were matched in respect of their age, weight and height and shown in the table -1. They were not significantly differed between them (P>0.05).

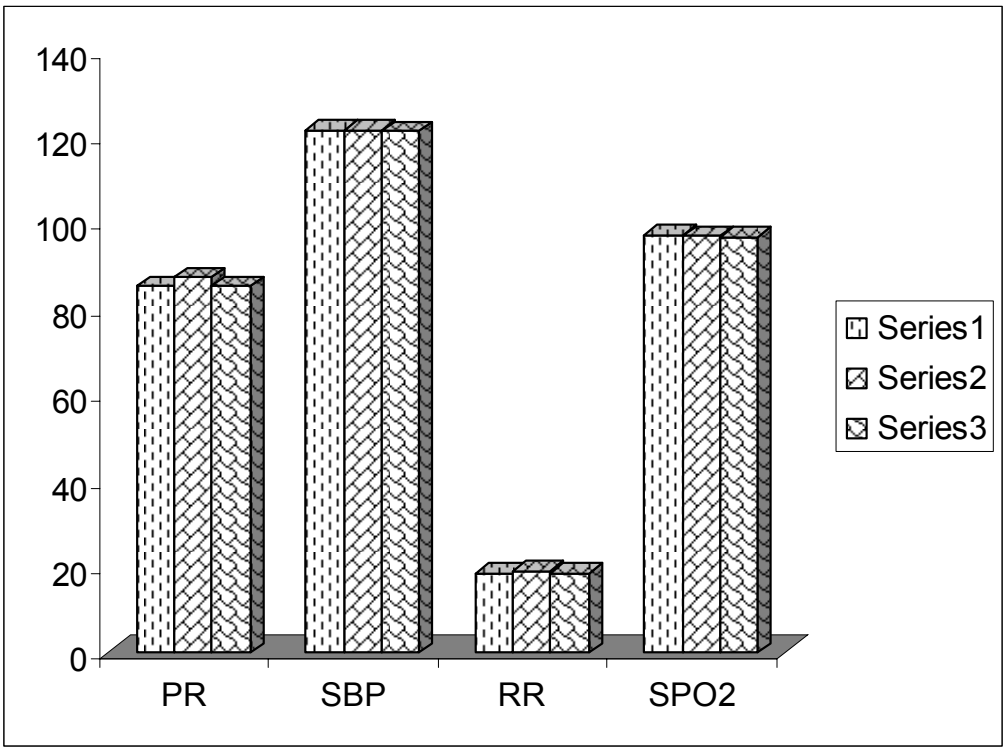


Table - 2 matching of three groups according to their Physiological characteristics

Variable	Group	n	Mean	SD	ANOVA 'F'	Df	Significance
Base PR	A	40	85.2	5.8	1.466	2,117	P>0.05
	B	40	87.3	7.2			
	C	40	85.2	5.9			
Base SBP	A	40	121.5	9.6	0.015	2,117	P>0.05
	B	40	121.6	10.2			
	C	40	121.2	7.9			
Base RR	A	40	18.4	1.0	2.831	2,117	P>0.05
	B	40	19.0	1.0			
	C	40	18.6	0.9			
Base SPO2	A	40	97.2	0.9	3.748	2,117	P>0.05
	B	40	96.9	1.0			
	C	40	96.6	0.8			

The Physiological characteristics of three groups were matched and stated in the above table -2. There was no significant differences were observed between groups in respect of their base Physiological characteristics (P>0.05).

Maximum Sensory level, Time and 2 Segment regression time:

The maximum sensory level and maximum time taken to reach the level were compared between three groups. The 2 segment regression time was also compared between the three groups.

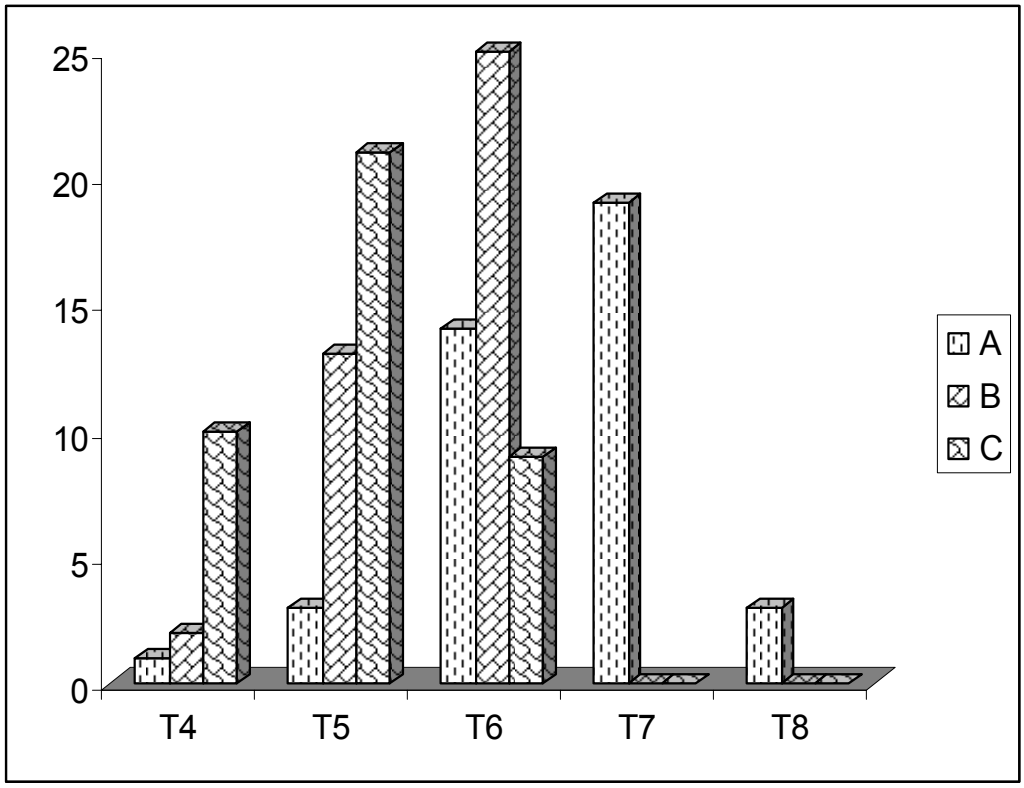


Table-3 Comparison of sensory level between three groups.

Max Sensory level	GROUPS				χ^2	df	Significance
	A	B	C	Total			
T4	1	2	10	13	76.795	8	P<0.001
T 5.	3	13	21	37			
T 6.	14	25	9	48			
T 7.	19	0	0	19			
T 8.	3	0	0	3			

The above table -3 associates the maximum sensory level of three groups.

The group A was associated with T_7, B was associated with T_6 and C was associated with T_5. The above associations were statistically very highly significant (P<0.001).

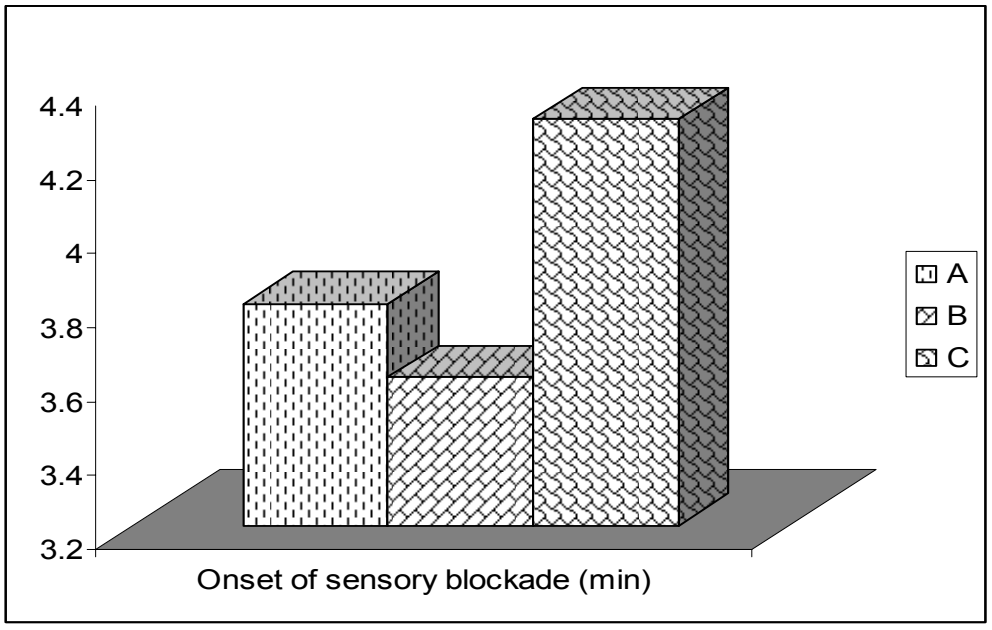


Table-4 Duration of time (minutes) to attain Sensory blockade or level between groups.

Groups	n	Mean	SD	ANOVA 'F'	d.f	Significance	Significantly differed groups
A	40	3.8	0.8	8.003	2,117	P<0.01	C differed with B and not differed with A. A&B not differed.
B	40	3.6	0.7				
C	40	4.3	0.8				

The sensory time between the groups were compared in the table-4. The mean time of A was 3.8±0.8 minutes with mean time of B (3.6±0.7) and C (4.3±0.8) not differed significantly (P>0.05). But the means of B (3.6±0.7) and C (4.3±0.8) were differed significantly (P<0.01).

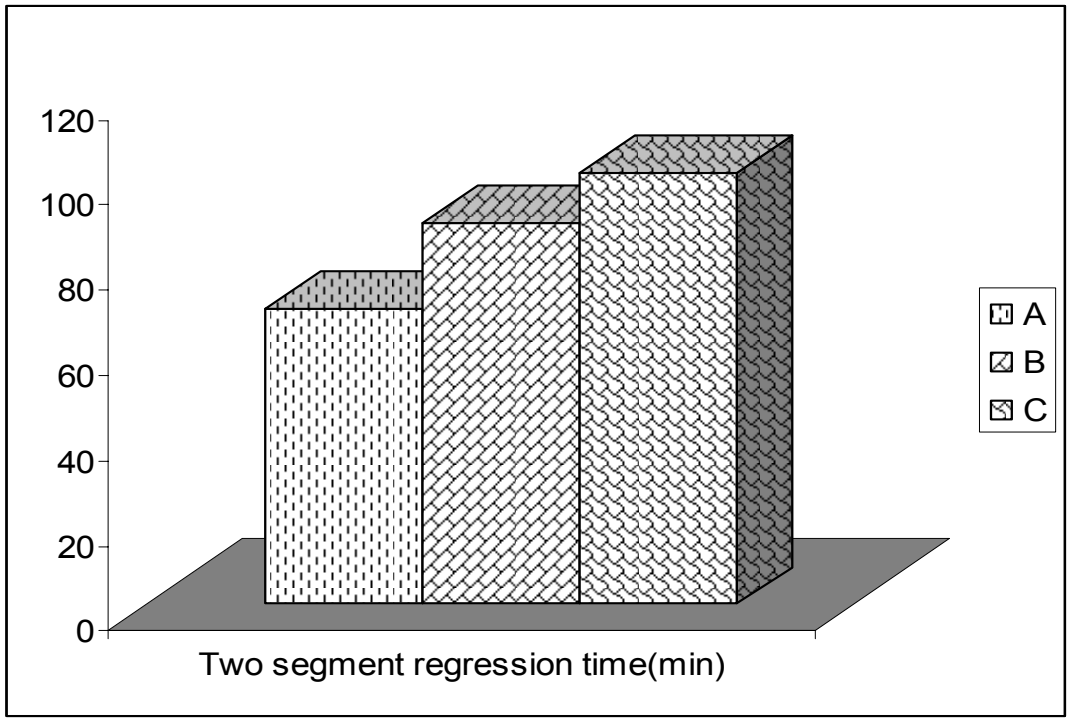


Table - 5 two segment regression time (minutes) to attain Sensory level between groups.

Groups	n	Mean	SD	ANOVA 'F'	d.f	Significance	Significantly differed groups
A	40	69.4	8.6	177.952	3,117	P<0.001	A,B&C were differed significantly between Them.
B	40	89.5	5.7				
C	40	101.1	8.1				

The two segment regression time between the groups were compared in the above table 5. The means of three groups were differed significantly between them (P<0.001).

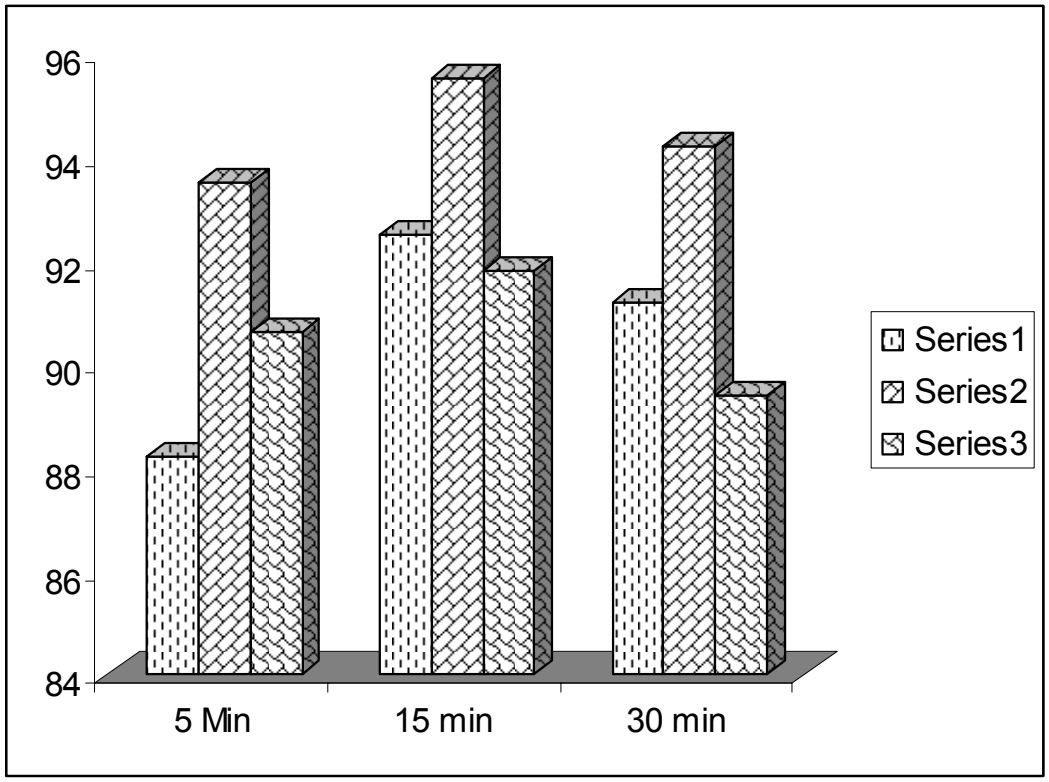


Table-6 Comparison of pulse rates between groups at different intervals.

Interval	Group	n	Mean	SD	ANOVA 'F'	df	Significance	Significantly differed groups
5 Min	A	40	88.2	7.6	4.370	3,117	P<0.01	A vs. B Significant AvsC, and BvsC not significant
	B	40	93.5	9.1				
	C	40	90.6	7.5				
15 Min	A	40	92.5	9.1	2.107	3,117	P>0.05	A,B & C were not significant
	B	40	95.5	8.5				
	C	40	91.8	8.3				
30 Min	A	40	91.2	6.7	5.012	3,117	P<0.01	A vs. B Not Signify B vs. C significant A vs. C Not Signify
	B	40	94.2	7.6				
	C	40	89.4	6.1				

The above table -6 shows the pulse rate at different intervals like at 5 minutes 15 minutes and 30 minutes. The group A was significantly differed with group B (P<0.05) and C was not significantly differed with groups A and C (P>0.05) at 5 minutes. At 15 minutes no significant difference was observed between the three groups (P>0.05). At 30 minutes B significantly differed with C (P<0.01) and at the same time A&B and A&C were not significantly differed (P>0.05).

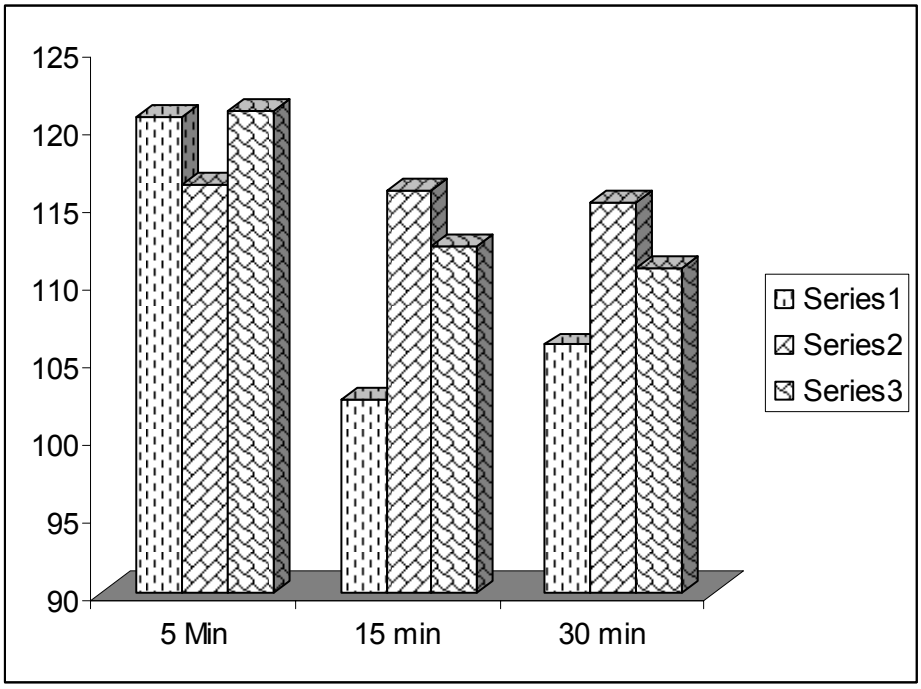


Table-7 Comparison of SBP between groups at different intervals.

Interval	Group	n	Mean	SD	ANOVA 'F'	df	Significance	Significantly differed groups
5 Min	A	40	120.6	11.4	2.136	3,117	P>0.05	Three groups were not differed significantly
	B	40	116.2	13.5				
	C	40	120.9	8.8				
15 Min	A	40	102.4	12.4	14.357	3,117	P<0.001	Significant. differed with B & C. but B & C not differed.
	B	40	115.8	9.9				
	C	40	112.2	12.0				
30 Min	A	40	105.9	12.5	7.838	3,117	P<0.01	A&B differed Sig. A&C and B&C not differed.
	B	40	115.1	9.7				
	C	40	110.8	8.4				

The SBP at different interval between the groups were shown in the above table-7. At 5 minutes, three groups were not significantly differed between them (P>0.05). At 15 minutes A significantly differed with the groups B and C (P<0.001). But B&C was not significantly differed between them (P>0.05). At 30 minutes A&B differed significantly (P<0.05). But A vs C and Bvs. C were not significantly differed (P>0.05).

Pain free time (minutes):

The pain free, the duration of time with out pain was analyzed between the three groups to identify in which group the pain was lasting.

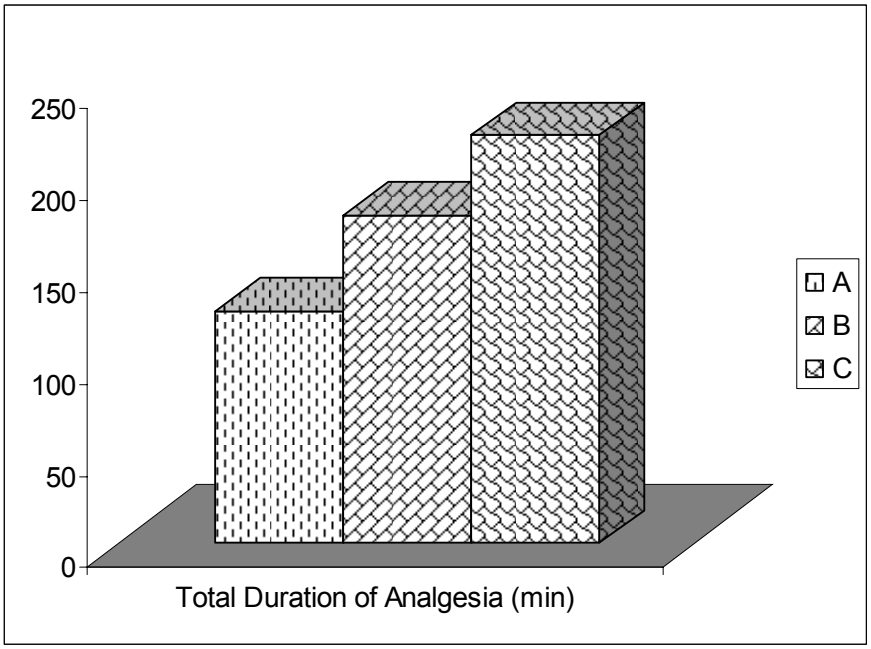


Table-8 Comparison of pain free time (minutes) between the groups.

Groups	n	Mean	SD	ANOVA 'F'	d.f	Significance	Significantly differed groups
A	40	125.8	23.1	177.955	3,117	P<0.001	All were differed significantly between them
B	40	178.2	14.4				
C	40	221.6	28.4				

The pain free time between the groups were compared in the above table 8. The means of three groups were 125.8±23.1, 178.2±14.4 and 221.6±28.4 respectively. They were significantly differed between them (P<0.001).

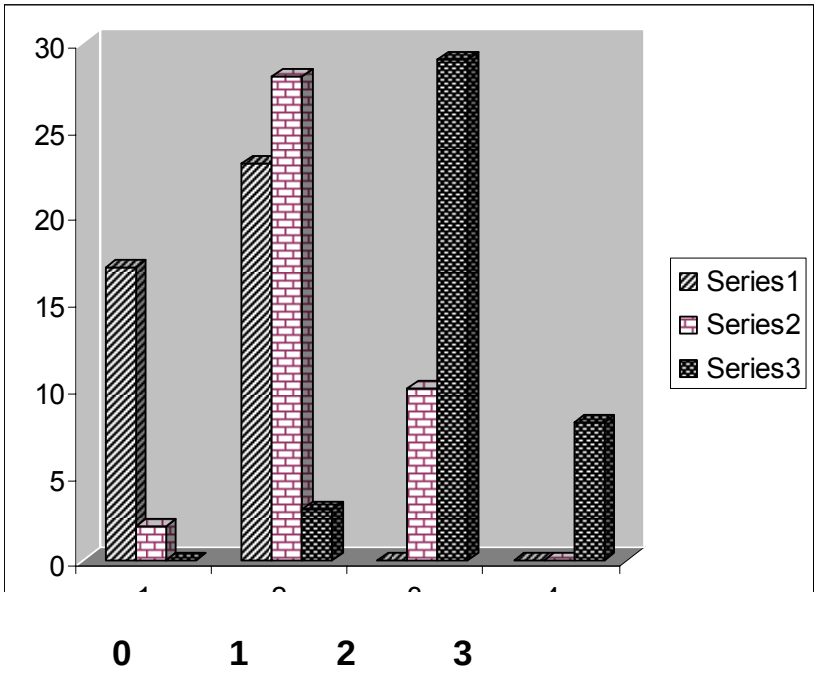


Table-9 Comparison of sedation between three groups.

Sedation level	GROUPS				χ^2	Df	Significance
	A	B	C	Total			
0	17	2	0	19	96.092	6	P<0.001
1	23	28	3	54			
2.	0	10	29	39			
3	0	0	8	8			
Total	40	40	40	120			

The sedation levels of three groups were associated in the above table-9. The sedation level 1 was associated with groups A and B. The sedation level 2 was associated with group C. The above associations were statistically very highly significant (P<0.001).

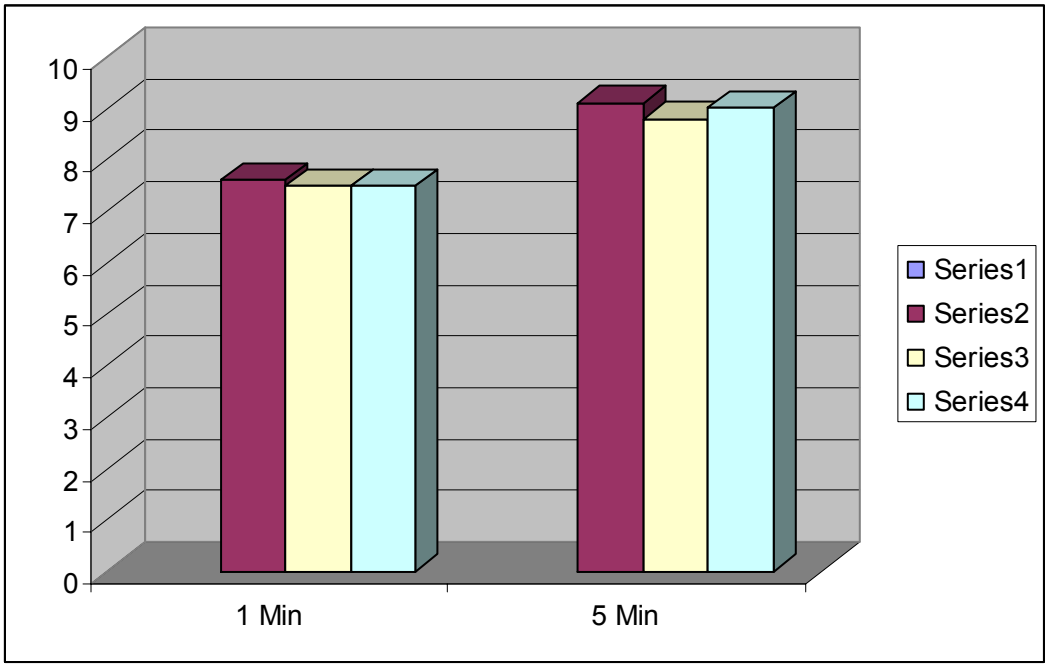


Table 10 Comparison of Apgar scores at 1 minute and 5minutes.

Time	Groups	n	Mean	SD	ANOVA 'F'	Df	Significance	Significantly differed groups
1 Min	A	40	7.6	0.5	0.122	3,117	P>0.05	All were not significant
	B	40	7.5	0.6				
	C	40	7.5	0.7				
5 Min	A	40	9.1	0.5	4.790	3,117	P<0.05	A & B only significant. Others NS
	B	40	8.8	0.5				
	C	40	9.0	0.3				

The Apgar score at 1 minute and 5 minutes were compared between the three groups in table 10. At 1 minute the Apgar were not significant between groups (P>0.05). At the Apgar scores of groups A&B was significantly differed (P<0.05). The others A&C and B&C were not statistically significant (P>0.05).

Inter-operative Complications

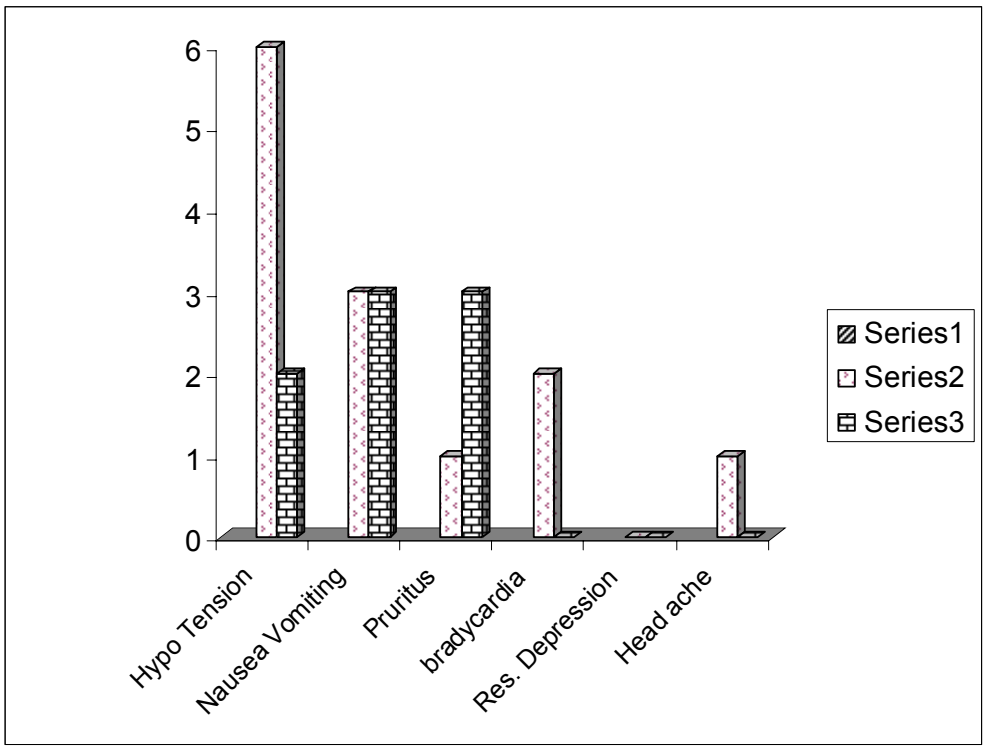
Nausea and vomiting occurred in 7.5% of all three groups. All were treated with inj. Metaclopromide.

Pruitus developed in only one patient i.e. 2.5% of group A patients.

In group B, 7.5% of patients developed pruitus.

In group C, 12.5% of patients developed pruritus

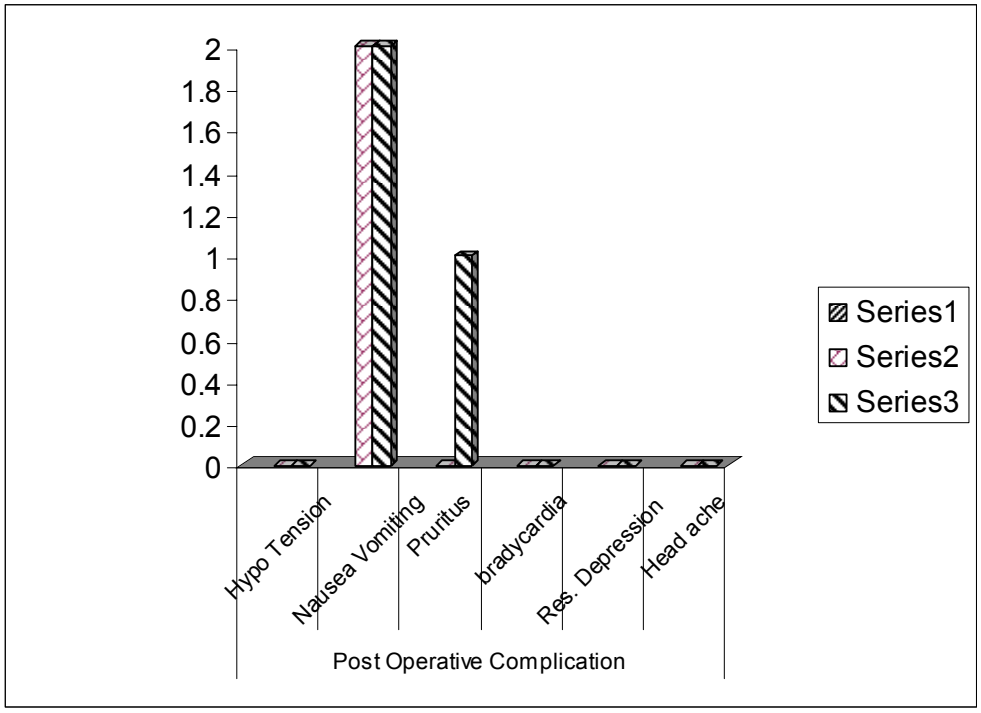
All were treated with inj. Chlorpheniramine maleate.



Post-Operative Complications

Nausea and vomiting occurred in 5% of patients in group A and group B and 2.5% in group C and they were treated with inj. Metaclopromide.

Pruritus occurred in 2.5% of patients in group B and 7.5% of patients in group C and they were treated with inj.chlorpheniramine maleate.


2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Hypo Tension
Nausea Vomiting
Pruritus
bradycardia
Res. Depression
Head ache
Post Operative Complication
Series1
Series2
Series3

DISCUSSIONS:

For Randomization, the three groups were matched with their age, height, weight, pulse, SBP, respiration and SPO2 and found that there was no significant difference between them (P>0.05). Hence, there groups were comparable groups. The sensory level T4 was obtained by A group 1(2.5%), B group 2(5%) and C group 10 (25%). The above attainment by C group was significantly greater than the other A& B groups (P<0.001). The mean time of C was significantly greater than B (4.3±0.8 > 3.6±0.7) and A and C were equal (4.3±0.8 = 3.8±0.8). The two segment regression time for C group was significantly more than B and the same for B was significantly more than A.(101.1±8.1 > 89.5 ± 5.7 > 69.4 ±8.6 and P<0.001).

The Pulse rate at 5 minutes of B group was significantly greater than A and C groups. (93.5 ±7.6 > 88.2±7.6 &90.6 ±7.5) and A group C group was equal (88.2±7.6 = 90.6 ±7.5). At 15 minutes, the pulse rates of three groups were more or less equal. (92.5±9.1 = 95.5±8.5 = 91.8=8.3 and P>0.05). At 30 minutes the pulse rate of C group was lesser than B group (89.4 ±6.1<94.2 ±7.6 and P<.0.01).
The same of A vs. B and A vs. C were more or less equal (91.2±6.7 = 94.2 ±7.6 and 91.2 ±6.7 = 89.4±6.1 and P>0.05).

The SBP at 5 minutes of three groups were 120.6 ±11.4, 116.2 ±13.5 and 120.9 ± 8.8 minutes respectively. The means were not significantly differed (P>0.05). At 15 minutes, the mean SBP of A group was 102.4 ± 12.4 and the same was significantly lower than B and C groups (102.4 ± 12.4 < 115.8 ± 9.9 & 112.2 ±12.0 and P<0.01). At 30 minutes, the mean SBP of B group was significantly higher than

B group (115.1± 9.7 > 105.9 ±12.5 and P<0.01). The mean SBP of A vs. C and B vs. C were not significant (P>0.05).

The pain free time of C group was significantly greater than B group and B group was significantly greater than A group (221.6 ±25.4 >178.2±14.4 >125.8±23.1and P<0.001).

The sedation level of A (57.5%) and B (70%) groups was associated with level 1 and C (72.5%) was associated with level 2. The improvement was very highly significant (P<0.001).

The Apgar score between the three groups was not significant at 1 Minute, But at 5 minutes, A group was significantly improved than B (9.1±0.5 > 8.8 ±0.5 and P<0.05). The A vs. C (9.1±0.5 = 9.0±0.3) and B vs.C (8.8 ±0.5= 9.0±0.3) were not significant (P>0.05).

From the above results and discussions the C group administration is better than the above two groups namely A and B groups.

- Evidences to conclude, improved quality of analgesia is the post-operative period (Paech M. J. et al).
- There is not of much difference in the onset of analgesia, similar to studies by Singh Harbhej et al.
- Two segment regression took longer time (C>B>A), similar to study conducted by Belzarena Sergio et al.
- Duration of analgesia increased (C>B>A), consistent with cong FC et al.

Hemodynamics

- There is less incidence of hypotension and Bradycardia, consistent with studies by Cang Fc, Chang PG et al.

Complications

- No respiratory depression occurred in any of these patients, consistent with study conducted by Lan et al.
- Pruritus developed in 12.5% in Group C, consistent with the study conducted by Cang Fc, Tsai YC et al.

Fetal Outcome

Low dose opiods do not have adverse effects on fetus and neonates (Ohen S, Arn et al) (Fernado F, Bonello E et al).

Conclusion

The above study bears out the following facts.

1. Intrathecal clonidine and the clonidine fentanyl combination, both improved quality of Intra Operative analgesia.
2. Combination of clonidine with fentanyl increased the intra operative analgesic efficacy and significantly prolonged post-operative analgesia compared with clonidine alone.
3. Stable Intra Operative hemodynamics was obtained.
4. Duration of analgesia was prolonged.
5. The incidence of side effects due to additive effects of the drugs was minimal.
6. Fetal outcome was not altered.

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COMPARATIVE EVALUATION OF ADDITION OF INTRATHECAL FENTANYL AND CLONIDINE ADDED TO 0.5% HYPERBARIC BUPIVACAINE FOR LOWER SEGMENT CAESAREAN SECTION

PROFORMA

CASE NO:

Name:	Age:	IP No:	Date:
Address:	Unit:	Wt:	Ht:
ASA:	Surgeon:	Anaesthetist:	Assessment No:

PRE OP STATUS

Inves

Hb:	B Urea: B Sugar: S creatinine:		
PR:	Bp:	Cvs:	Rs:

PRE MEDICATION

Pre loading: Yes/No	Type of fluid:		Amount given
Position for SAB:	Level of Inj.	Time of Inj.	Drug &Dose given:

PARAMETERS STUDIED

Time of onset of sensory block and level –

Grade of motor block –

Two segment regression time

Level of block at the end of surgery

Subarachnoid block – Delivery interval

Uterine incision and delivery interval

APGAR score: 1min - 5min –

Duration of postoperative analgesia –

INTRAOPERATIVE MONITORING

TIME	SENSORY LEVEL	VAS	PULSE RATE	BP	SPO2	RESPIRATORY RATE	SEDATION SCORE	REMARKS
5 min 10min 15min 30min 45min 1hr								

COMPLICATIONS

HYPOTENSION	BRADY CARDIA	PRURITIS	NAUSEA & VOMITING	MUSCLE RIGIDITY	COMPLICATIONS OF BABY	RESP.	NIL

POSTOPERATIVE MONITORING

TIME	SENSORY LEVEL	VAS	PAINFREE INTRAVAL	REMARKS
2hr 4hr 6hr				

MASTER CHART																						
MASTER CHART GROUP A					BASELINE				Max	Time	2 seg	Motor	PR			BP			Sed Score	Pain Free	APGAR	
SL.NO	NAME	AGE	WT	HT	PR	BP	RR	SPO2	Senlev	Max Sen	Reg time		5 min	15 min	30 min	5 min	15 min	30 min			1 min	5 min
1	Maharasi	33	54	153	82	120	20	98	7	3	78	3	86	93	94	120	98	104	1	141	8	9
2	Mantram	23	59	154	94	130	18	97	7	3	69	3	106	108	108	130	102	114	1	111	7	9
3	Farida	18	63	162	80	120	18	97	7	2	75	3	84	104	106	120	130	130	1	133	7	9
4	Murugama	19	56	151	93	110	18	98	7	4	64	3	96	104	93	110	90	104	0	100	7	10
5	Sudali	27	62	149	86	120	19	97	6	3	78	3	90	97	90	120	92	108	0	123	7	9
6	Devi	23	57	153	99	130	21	98	7	4	66	3	104	108	98	130	110	118	0	104	8	10
7	Selvi	22	57	154	78	140	19	98	7	4	65	3	84	89	88	140	120	126	0	108	7	10
8	Kalayani	26	59	159	78	110	18	98	6	4	58	3	82	93	90	110	90	102	1	100	8	10
9	Malai	27	60	153	82	130	18	97	7	4	56	3	84	96	90	130	120	126	1	91	8	10
10	Lakshmi	22	63	168	82	120	18	97	6	4	76	3	84	90	90	120	80	84	0	142	7	10
11	Kokila	27	63	159	93	130	18	95	7	4	75	3	97	99	88	130	102	100	1	138	8	9
12	Kumudava	21	55	150	93	140	17	96	6	4	55	3	96	96	84	140	120	120	1	93	8	9
13	Paichiamma	25	59	158	78	130	18	97	7	3	80	3	84	84	90	130	108	110	0	158	7	9
14	Muthu	23	49	168	84	110	19	97	7	3	69	3	86	93	104	110	108	118	0	123	8	9
15	Sankaramm	32	59	151	82	110	18	98	5	5	77	3	88	93	90	110	90	98	1	135	8	9
16	Sumathy	30	68	151	84	120	17	96	6	5	58	3	86	93	88	120	104	108	1	100	8	9
17	Gomathi	22	56	152	92	140	18	96	5	5	66	3	98	102	98	140	100	108	1	124	8	9
18	Muthulaksh	35	54	156	78	120	18	96	7	3	70	3	82	86	89	120	94	98	1	106	7	9
19	Palammal	25	61	153	78	120	19	97	6	4	66	3	60	74	80	84	92	110	0	139	8	9
20	Selvei	32	59	147	88	130	17	95	5	4	60	3	92	94	90	130	110	110	1	118	7	8
21	Mariaamal	22	68	153	88	110	18	97	7	3	60	3	84	89	90	110	116	104	1	101	7	8
22	Jagada	22	63	162	77	110	17	96	6	4	69	3	84	88	86	110	90	94	1	143	7	8
23	Sasi	27	59	162	82	110	18	97	7	3	81	3	88	93	91	110	100	106	0	174	7	9

24	Judi	22	68	156	88	130	20	96	7	3	78	3	90	54	82	130	110	110	1	136	8	9
25	Subbamal	22	53	149	86	110	18	97	6	5	74	3	86	92	92	110	92	70	0	130	7	10
26	Ramalaka	22	52	142	82	110	18	97	4	4	73	3	84	86	72	110	80	76	1	151	8	9
27	Sujatha	29	68	158	88	130	19	97	6	5	58	3	90	94	90	130	86	94	1	105	8	9
28	Kayal	24	64	158	78	120	19	98	6	5	84	3	80	84	86	120	90	98	1	147	8	9
29	Fathima	28	55	156	82	120	18	98	7	5	72	3	88	90	88	120	110	118	1	134	8	9
30	Babitha	23	48	147	82	110	19	98	6	4	80	3	88	93	90	110	110	100	1	143	7	9
31	Jenifrer	22	52	156	92	110	21	98	6	4	68	3	96	98	93	110	90	94	0	139	7	9
32	Gomathi	20	52	154	86	120	18	97	7	5	81	3	89	93	102	120	114	110	0	162	8	9
33	Pattu	21	56	153	84	120	20	98	6	4	84	3	86	93	92	120	100	106	0	186	8	9
34	Kalayni	26	55	158	82	120	20	98	7	4	56	3	84	88	89	120	110	110	0	92	8	9
35	Rajeshwari	21	59	153	88	130	19	98	6	5	56	3	88	93	94	130	110	118	1	98	7	10
36	Essakiamm	19	59	162	93	140	18	97	8	4	58	3	96	97	98	140	130	120	1	102	8	9
37	Papa	25	56	156	84	120	17	98	7	3	75	3	86	93	90	120	96	100	0	131	8	9
38	Marriamma	24	59	168	82	110	18	98	8	4	68	3	88	90	86	110	110	106	0	126	7	10
39	Maharasi	35	57	159	93	130	18	97	8	3	69	3	98	102	98	130	100	110	1	116	7	9
40	Santha	20	63	169	84	120	19	98	7	3	73	3	86	93	90	120	94	96	0	131	8	10

MASTER CHART																						
MASTER CHART GROUP B					BASELINE			Max	Time		2 seg	Motor	PR			BP		Sed Score		Pain Free	APGAR	
SL.NO	NAME	AGE	WT	HT	PR	BP	RR	SPO2	Senlev	Max Sen		Reg time		5 min	15 min	30 min	5 min	15 min	30 min			1 min	5 min
1	Arumuga	22	55	154	84	110	19	97	3	90		3	89	84	88	108	110	114	2	170	7	9	
2	Valarmat	27	48	154	88	130	19	97	4	100		3	98	98	82	90	112	114	2	195	7	8	
3	Priya	32	62	165	90	120	20	98	3	80		3	120	120	118	110	110	110	1	145	7	8	
4	Latha	22	48	152	90	110	20	99	3	70		3	92	91	93	110	100	90	1	163	8	9	
5	Kanaka	20	56	159	88	130	20	98	3	83		3	88	78	74	130	124	126	2	160	7	8	
6	Sudha	20	59	153	82	140	19	96	2	90		3	99	104	102	130	130	128	2	191	7	8	
7	Subbu	22	57	149	82	130	21	96	5	95		3	71	82	108	80	100	110	1	192	8	10	
8	Kanni	20	80	159	82	130	20	97	5	86		3	83	78	88	130	128	126	2	169	8	10	
9	Mupudath	27	82	159	88	120	21	96	3	91		3	82	88	93	130	122	132	1	172	7	8	
10	Anbu	21	78	156	97	130	20	97	4	92		3	98	93	92	118	130	128	1	183	8	9	
11	Kumudav	30	63	153	80	130	20	97	4	82		3	86	92	93	128	128	124	1	163	8	9	
12	Paichiam	20	63	151	88	120	20	98	4	88		3	96	102	93	132	128	116	1	175	8	9	
13	Muthu	25	62	149	88	120	19	97	3	83		3	93	98	88	126	132	122	1	175	8	9	
14	Sankara	25	57	154	84	140	18	99	5	87		3	98	92	98	122	130	118	1	174	7	8	
15	Sumathy	23	62	156	88	120	19	98	4	92		3	93	98	89	122	120	128	1	180	7	9	
16	Gomathi	32	59	153	80	120	18	97	3	82		3	86	92	93	122	112	112	1	165	7	9	
17	Muthulak	20	62	154	93	120	18	97	4	92		3	97	102	102	112	110	110	1	172	8	9	
18	Sudali	30	54	153	80	120	18	97	4	84		3	84	86	93	118	108	112	1	169	7	9	
19	Nila	27	55	147	82	114	18	97	3	92		3	78	92	96	104	114	118	1	172	8	9	
20	Dhanam	20	57	149	96	130	20	98	4	86		3	102	100	97	132	116	122	1	169	8	9	
21	Valli	24	74	156	86	110	17	96	2	89		3	96	104	88	100	106	100	1	177	7	9	
22	Lakshmi	23	48	147	88	100	18	95	3	94		3	104	104	102	94	94	96	1	190	7	9	

23	Sangeetha	25	48	149	86	110	19	97	4	88	3	106	108	98	98	110	106	2	173	8	9	
24	Perumal	21	57	147	92	120	19	97	4	95	3	106	108	104	110	108	110	1	170	7	9	
25	Eassakith	28	68	159	93	110	19	97	4	89	3	104	93	94	104	112	112	1	183	8	9	
26	Parumu	21	62	154	84	110	19	95	4	94	3	93	106	98	108	104	108	2	186	8	9	
27	Susi	27	59	153	93	120	19	96	3	88	3	104	93	102	110	112	110	1	182	8	9	
28	Ganapath	23	62	156	78	110	19	96	4	89	3	90	100	89	118	108	110	1	172	7	9	
29	Syed	25	54	154	82	140	18	96	4	92	3	93	93	88	130	120	130	1	171	7	8	
30	Santhana	24	56	152	86	130	19	97	4	89	3	92	94	96	132	118	120	1	173	7	9	
31	Subbu	22	65	153	86	140	19	96	5	91	3	98	96	88	140	122	128	0	188	8	8	
32	Rekha	27	48	152	88	120	19	96	3	92	3	96	92	97	108	110	110	1	183	8	9	
33	Kalai	30	59	151	93	130	17	95	3	88	3	98	99	104	130	120	120	0	172	7	9	
34	Sugu	21	68	159	89	110	19	97	4	92	3	98	100	93	120	120	116	1	200	7	8	
35	Pavai	19	52	152	88	110	19	96	3	94	3	94	99	90	100	100	98	1	178	7	9	
36	Viji	22	60	158	82	130	18	98	3	86	3	84	98	94	118	128	116	1	183	7	9	
37	Alibath	28	54	162	82	120	21	98	4	92	3	88	92	94	114	124	118	1	171	7	9	
38	Mohana	26	57	159	78	130	18	97	3	94	3	80	92	84	130	120	120	2	182	8	9	
39	Thai	22	53	159	93	110	17	98	3	103	3	96	82	94	110	106	106	2	228	9	10	
40	Mari	20	54	159	84	120	18	98	3	95	3	88	98	90	120	124	108	2	214	8	9	

MASTER CHART																						
MASTER CHART GROUP C					BASELINE				Max	Time	2 seg	Motor	PR			BP			Sed Score	Pain Free	APGAR	
SL.NO	NAME	AGE	WT	HT	PR	BP	RR	SPO2	Senlev	Max Sen	Reg time		5 min	15 min	30 min	5 min	15 min	30 min			1 min	5 min
1	Sumathai	27	52	164	88	120	21	99	4	101	3	88	90	84	120	110	110	2	220	7	9	
2	Kalai	25	63	154	88	110	21	98	2	105	3	92	86	89	110	110	110	2	218	7	9	
3	Prema	27	60	160	98	110	19	96	4	104	3	106	104	96	116	104	106	2	207	8	9	
4	Kavitha	21	54	153	88	120	19	96	5	104	3	108	114	108	108	120	120	2	217	7	8	
5	Sangetha	21	48	153	92	130	20	97	4	94	3	104	82	84	132	120	120	3	203	8	9	
6	Pradeepa	21	54	153	84	120	18	96	4	107	3	93	96	88	124	114	108	2	242	7	9	
7	Devi	26	63	156	90	130	18	96	5	94	3	92	94	88	130	120	120	2	206	8	9	
8	Vadivoo	25	72	168	88	110	18	95	5	98	3	96	96	89	110	104	106	2	294	7	9	
9	Kuthalam	25	59	156	78	120	19	98	5	98	3	88	88	85	124	112	108	2	215	8	9	
10	Kalayni	22	63	151	88	120	19	96	4	99	3	96	96	88	124	116	114	2	211	7	9	
11	Rajeshwari	29	68	159	88	130	18	96	5	102	3	88	96	84	130	118	122	2	205	8	9	
12	Essakiamm	32	57	156	84	110	20	97	4	98	3	96	102	98	106	112	110	2	244	8	9	
13	Papa	22	54	151	78	130	20	97	5	109	3	90	94	88	130	120	120	3	215	8	9	
14	Marriamm	29	45	154	92	130	19	97	5	98	3	104	59	84	116	84	106	3	211	8	9	
15	Maharasi	21	58	153	80	130	18	95	4	109	3	86	90	88	128	132	120	2	239	7	9	
16	Dhanam	26	62	162	78	130	19	97	4	104	3	88	84	82	130	118	120	3	222	7	9	
17	Rosy	23	50	156	92	110	18	97	5	92	3	96	98	102	110	70	86	2	256	7	9	
18	Suleka PV	30	56	147	78	120	17	96	5	109	3	82	88	84	120	108	100	2	168	8	9	
19	Subbu	22	68	176	82	130	17	97	3	83	3	88	93	93	130	118	122	2	240	8	9	
20	Kanni	20	64	159	82	130	19	97	5	108	3	86	92	98	130	118	120	2	266	7	9	
21	Mupudathi	21	69	156	88	130	20	97	5	112	3	93	97	88	130	112	114	2	205	7	9	
22	Anbu	30	59	156	93	120	18	96	3	98	3	102	104	98	120	130	118	1	255	8	9	
23	Kumudava	25	51	146	92	110	18	96	5	117	3	90	88	83	110	96	98	3	211	7	9	
24	Mari Priya	27	62	158	74	130	18	96	4	88	3	79	84	86	130	118	120	1	172	7	9	

25	Vishalathc	25	63	169	82	130	18	97	4	94	3	88	93	92	130	134	118	2	218	8	9	
26	Jothi	23	68	153	78	120	19	96	4	104	3	86	88	83	124	108	110	2	190	7	9	
27	Kanmani	32	62	156	88	120	18	97	4	95	3	73	96	94	120	108	110	2	220	8	9	
28	Kaviya	23	59	163	82	110	18	95	5	112	3	86	93	92	110	102	100	3	216	8	9	
29	Kiruthika	30	64	158	93	120	18	96	4	98	3	96	98	93	124	118	108	2	246	8	9	
30	Maheswar	29	59	154	82	120	18	97	2	89	3	86	90	88	120	102	102	3	205	7	9	
31	Malathi	27	73	169	88	130	18	97	5	82	3	92	93	88	130	118	120	1	181	8	9	
32	Meera	24	63	156	78	120	19	97	3	96	3	80	83	78	120	118	106	2	174	8	9	
33	Bhagyam	30	59	153	74	130	18	96	5	113	3	83	86	86	130	118	122	2	194	7	9	
34	Pattu	20	68	159	92	120	18	96	4	99	3	93	94	98	120	124	108	2	253	7	9	
35	Kalayni	28	62	159	82	120	18	96	4	104	3	86	90	88	120	126	110	2	225	8	9	
36	Rajeshwar	22	41	145	80	110	18	97	5	110	3	82	84	82	104	104	104	2	218	8	10	
37	Essakiam	20	48	147	82	110	19	97	5	112	3	90	92	88	116	104	102	2	245	7	9	
38	Bharkavi	23	59	153	82	130	18	98	4	104	3	86	88	86	120	100	104	2	251	7	9	
39	Latha	29	64	161	92	120	18	97	5	98	3	96	96	94	130	110	110	2	284	8	10	
40	Jaya	33	63	159	88	110	18	97	4	104	3	90	93	90	100	110	100	3	201	7	9	